Review Paper

A Systematic Review on the Risk Factors of Steroid-sensitive Nephrotic Syndrome Relapse in the Pediatric Population

Mahmoud Yousefifard[1], Koohyar Ahmadzadeh[1], Arian Madani Neishaboori[1], Seyedeh Niloufar Rafiei Alavi[1], Seyedeh Romina Rafiei Alavi[2], Hooman Ahmadzadeh[3], Amirmohammad Toloui[1], Mohammed I M Gubari[4], Michael E. Jones[5], Nematollah Ataei[6], Mojtaba Fazel[6], Mostafa Hosseini[6,7*]

1. Physiology Research Center, Iran University of Medical Sciences, Tehran, Iran.
2. Department of Medicine, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran.
3. Department of Medicine, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran.
4. Department of Community Medicine, College of Medicine, University of Sulaimani, Sulaimani, Iraq.
5. Division of Genetics and Epidemiology, The Institute of Cancer Research, London, UK.
6. Pediatrics Chronic Kidney Disease Research Center, Tehran University of Medical Sciences, Tehran, Iran.
7. Department of Epidemiology and Biostatistics, School of Health, Tehran University of Medical Sciences, Tehran, Iran.

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Citation Yousefifard M, Ahmadzadeh K, Madani Neishaboori A, Rafiei Alavi SN, Rafiei Alavi SR, Ahmadzadeh H, et al. A Systematic Review on the Risk Factors of Steroid-sensitive Nephrotic Syndrome Relapse in the Pediatric Population. Journal of Pediatrics Review. 2024; 12(2):153-170. http://dx.doi.org/10.32598/jpr.12.2.1190.1

http://dx.doi.org/10.32598/jpr.12.2.1190.1

Article info:
Received: 17 Jan 2024
First Revision: 26 Feb 2024
Accepted: 16 Mar 2024
Published: 01 Apr 2024

Key Words:
Nephrotic syndrome, Steroi-sensitive nephrotic syndrome (SSNS), Risk factor, Recurrence

ABSTRACT

Background: Identifying affecting and predictive factors of steroid-sensitive nephrotic syndrome's (SSNS's) outcome may greatly benefit the proper management of SSNS patients.

Objectives: The current systematic review comprehensively reviews all available evidence on the risk factors of SSNS relapse in children and adolescents.

Methods: An extensive search was conducted on the electronic databases of Medline, Embase, Web of Science, and Scopus until February 18, 2024. Studies investigating the risk factors of relapse were included in this systematic review.

Results: A total of 11 articles were included. Age, gender, and laboratory variables, such as serum creatinine and serum protein are not risk factors for relapse in these studies. Possible associations were reported for risk factors, such as the number of relapses and response time. Overall, the studies reported conflicting results on the value of relapse risk factors.

Conclusions: Although factors, such as hematuria, hypertension, time from treatment to response, and number of relapses have been proposed as possible risk factors for relapse, no conclusion can be reached due to the heterogeneity of studies. Future studies should have more conforming designs to make comparisons more reliable.

** Corresponding Author:*
Mostafa Hosseini, Professor.
Address: *Department of Epidemiology and Biostatistics, School of Health, Tehran University of Medical Sciences, Tehran, Iran.*
Tel: *+98 (21) 88989125.*
E-mail: *mhossein110@yahoo.com*

Introduction

Nephrotic syndrome is a collection of symptoms caused by kidney injury. These symptoms include proteinuria, decreased serum albumin level, elevated serum lipids, and edema [1, 2]. The most efficient treatment for nephrotic syndrome is corticosteroid therapy, and the patients are divided into four groups steroid sensitive, steroid-resistant, steroid-tolerant, and steroid-dependent based on their response to treatment [3, 4].

Steroid-sensitive nephrotic syndrome (SSNS), which affects a large proportion of patients, is defined as the response to corticosteroid therapy within the first eight weeks of the treatment. Although patients with SSNS have a good prognosis, 40% to 50% of them experience multiple relapses or become steroid-dependent [1-4]. These patients suffer from several complications, such as the Cushing symptoms, hypertension, elevated serum lipid level, hyperglycemia, severe infections, growth retardation, and osteopenia [5].

Identifying affecting and predictive factors of SSNS outcomes may greatly aid physicians in proper patient management. Several available studies have reported possible risk factors and predictive factors of adverse outcomes in patients with nephrotic syndrome. For instance, Mishra et al. [6] have shown that patients aged between 1 and 3 years old have a higher risk of relapse; however, Bakr et al. [7] reported no relation between patients' age at debut and relapses. Ali et al. [8] have demonstrated that hematuria at debut may be a risk factor for relapse. However, Noer [9] have not reported a predictive value for hematuria. Discrepancies can also be seen in reports on the predictive value of hypertension [9, 10] and time from treatment to response [8, 9].

The currently existing evidence on the risk factors of SSNS relapse is inconsistent, and no conclusion has been reached in this regard. This study adopts a systematic approach and gathers available evidence on the risk factors of SSNS relapse in children and adolescents.

Methods

Study design

The current study was designed to investigate the risk factors of SSNS relapse in the pediatric and adolescent populations. The patient, exposure, comparison, and outcome framework in the present study was defined as follows: Patients (P) described children and adolescent patients with SSNS; exposure (E) showed risk factors of frequent relapse or relapse; comparison (C) demonstrated infrequently relapsing nephrotic syndrome (IFRNS) patients or non-relapsing patients; and outcome (O) showed SSNS frequent relapse or relapses. Two reviewers independently performed all study steps, and a third reviewer was consulted in case of disagreement.

Search strategy

A search was conducted on the electronic databases of Medline, Embase, Web of Science, and Scopus until February 18th, 2024. Relevant keywords were selected through Emtree terms of Embase database and MeSH terms of PubMed gateway, consultation with the experts, and review of related studies. Moreover, grey literature was addressed by a manual search in Google and Google Scholar search engines and forward (citation tracking) and backward (reference tracking) screening. Supplementary Material 1 shows the utilized search strategies.

Selection criteria

The observational studies investigating the value of patient baseline and clinical characteristics in predicting SSNS relapse were included. The target population was children and adolescents under 18 years old without language, location, racial or sexual limitations.

Articles not having a no-relapse group, not assessing relapse as an outcome, not reporting data collection protocol, articles without accurate definitions of the relapse, studies with mixed adult and pediatric populations with no stratification of the results by age group, case reports, and review articles were excluded from this study.

Data extraction

Two independent reviewers screened and selected articles based on the inclusion and exclusion criteria. Data from the included articles were summarized using a checklist based on preferred reporting items for systematic reviews and meta-analyses statement protocols [11]. The extracted data included study design, sample size, number of patients in relapse and non-relapse groups, follow-up, studied risk factors, reported data for each risk factor, and definitions of nephrotic syndrome, SSNS, relapse, and frequent relapse. Studied risk factors included patient characteristics (age at debut, gender), hematuria at debut, serum creatinine, serum albumin, serum cholesterol, serum protein, urine 24 h protein)

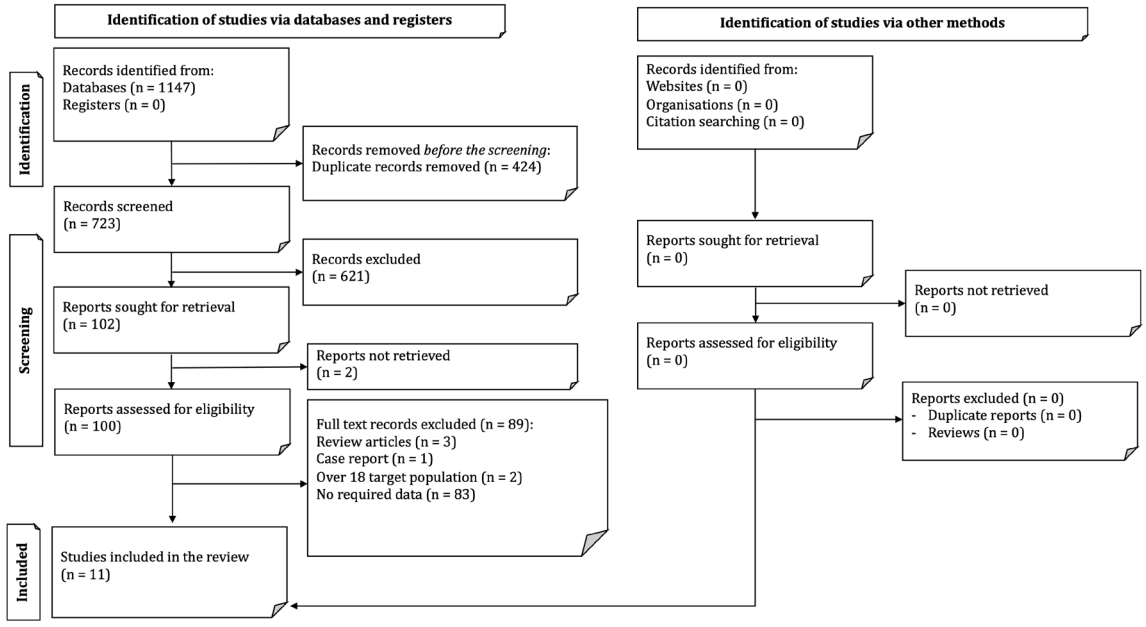

Figure 1. Study selection flowchart

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blood pressure/pre-existing hypertension, and disease characteristics (number of relapses, time to response). Any disagreements in the screening or data extraction processes were resolved by consulting a third reviewer.

Quality assessment and certainty of evidence

The quality of the included studies was evaluated using National Heart, Lung, and Blood Institute (NHLBI) protocols. Two independent researchers performed the quality assessment, and disagreements were resolved using the third reviewer's opinion. The NHLBI quality control checklists are available at NHLBI. Certainty of evidence was assessed using the grading of recommendations, assessment, development, and evaluation framework [12].

Terms definitions

Nephrotic syndrome was defined as massive proteinuria, hypoalbuminemia, edema, and hypercholesterolemia. SSNS was defined as a response within 8 weeks of steroid therapy. Relapse was defined as proteinuria for more than 3 consecutive days. Frequent relapse was defined as ≥2 relapses in the first 6 months and ≥4 relapses in 12 months. Hematuria was microscopic (≥5 red blood cells/high power field). However, studies used different definitions and guidelines provided in Supplementary Tables 1 and 2.

Data synthesis

Studies have compared frequently relapsing nephrotic syndrome (FRNS) patients with IFRNS and reported risk factors of frequent relapse, or compared relapsing patients with non-relapsing patients and reported risk factors of relapse. Accordingly, this article's results section separately reports each comparison's results.

The reported data for qualitative variables, such as gender, were recorded as the number of patients with or without risk factors. All continuous variables, such as serum creatinine, were converted into Mean±SD to ease the comparison of study reports. Few studies have reported summary statistics, such as odds ratio (OR) and hazard ratio (HR). For studies without reports of summary statistics, OR and 95% confidence interval (95% CI) were calculated to ease the comparison of study reports.

Results

Study characteristics

The systematic search resulted in 723 non-duplicate records. After the initial title and abstract screening, 102 articles were studied in more detail. Two articles were not retrieved [13, 14]. Finally, 11 articles were included in the present systematic review (Figure 1) [6-10, 15-20]. The included articles were designed as eight cohort studies and three longitudinal and case-control studies.

Table 1. Characteristics of included studies

	Author, Year, Country	Study Type	Design	Sample Size	Relapse Case	Non-Relapse	Number of Males	Follow-up Duration (Month)	Studied Factor
FRNS Versus IFRNS	Cetin et al. 2019, Turkey [15]	Case-control	Retrospective	32	16	16	22	NR	Age, gender, duration of treatment, number of relapses
	Fan et al. 2015, China [16]	Cohort	Retrospective	22	10	12	NR	18	Age, gender, serum albumin, serum cholesterol, mean arterial pressure
	Ali et al. 2016, Iraq [8]	Cohort	Retrospective	80	45	35	55	12	Age, gender, hematuria, serum creatinine, duration of treatment, time to response
	Kabuki et al. 1998, Japan [17]	Cohort	Retrospective	60	15	45	45	120	Age, gender, number of relapses
	Nakanishi et al. 2013, Japan [18]	Case-control	Retrospective	138	32	106	98	12	Age, gender, serum albumin, serum cholesterol, serum protein, time to response, time to first relapse
	Noer, 2005, Indonesia [9]	Cohort	Prospective	25	10	15	NR	12	Age, gender, hematuria, hypertension, time to response
	Zhaoyang et al. 2023, China [10]	Longitudinal	Prospective	92	10	82	70	NR	Age, gender, hypertension, serum creatinine, urine 24 h protein
Relapse Versus No-relapse	Bakr et al. 2009, Egypt [7]	Cohort	Prospective	26	15	11	19	NR	Age, gender, blood pressure, serum creatinine, serum albumin, serum cholesterol, urine 24 h protein
	Esezobor et al. 2016, Nigeria [19]	Cohort	Retrospective	50	23	27	34	24	Age, gender, hematuria, hypertension, serum creatinine
	Mishra et al. 2013, India [6]	Cohort	Retrospective	150	61	89	108	12	Age, gender, hematuria, hypertension, serum albumin, serum cholesterol, time to response, infection at presentation
	Takeda et al. 1996, Japan [20]	Cohort	Retrospective	48	NR	NR	32	NR	Age, serum protein

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Abbreviations: FRNS: Frequently relapsing nephrotic syndrome; IFRNS: Infrequently relapsing nephrotic syndrome; NR: Not reported.

Studies have investigated patients with FRNS vs IFRNS [8-10, 15-18] and relapsers vs non-relapsers [6, 7, 19, 20]. Studies evaluated possible risk factors of relapse, such as patient characteristics including gender, age, hematuria, blood pressure, creatinine, albumin, serum protein, serum cholesterol, urine 24 h protein, and disease characteristics, including duration of treatment, time to response, and number of relapses. Table 1 presents the characteristics of the included studies.

FRNS versus IFRNS

Seven articles (449 patients, 30.7% of patients experienced frequent relapses) evaluated the risk factors of frequent relapse (Table 2). Studies showed that age at debut and gender are not risk factors for frequent relapse. Ali et al. [8] demonstrated that hematuria at debut could be a risk factor for frequent relapse (OR=6.70; 95% CI, 1.40%, 32.09%), while Noer [9] did not report the same findings (OR=3.50; 95% CI, 0.27%, 44.95%). Noer also demonstrated that hypertension can be a risk factor for frequent relapse (OR=32.67; 95% CI, 2.85%, 374.13%); however, the wide confidence interval is an important limitation. Zhaoyang et al. [10] did not report the same findings for hypertension (OR=4.44; 95% CI, 0.37%, 54.00%). Mean arterial blood pressure was not a risk factor for frequent relapse [16]. Serum creatinine, serum albumin, serum cholesterol, and serum protein at debut and urine 24 h protein were not shown to be risk factors for frequent relapse.

Cetin et al. [15] demonstrated that a longer duration of treatment can be a risk factor for frequent relapse (OR=308.93; 95% CI, 47.99%, 1988.82%) while Ali et al. [8] did not report the same findings. Studies demonstrated that a longer time from treatment to response could be a risk factor for frequent relapse, however, results had varying thresholds [8, 9, 18]. Nakanishi et al. [18] reported that time to the disappearance of proteinuria ≥9 days could be a risk factor for frequent relapse (HR=3.09; 95% CI, 1.42%, 7.27%), while Ali et al. [8] and Noer [9] demonstrated that a time to response between 2 to 4 weeks (OR=17.25; 95% CI, 3.69%, 80.65%, reference: <2 weeks) and a shorter time to response (OR=6; 95% CI, 1.01%, 35.91%) could be a risk factor of frequent relapse, respectively. Nakanishi et al. [18] also

Table 2. Risk factors of SSNS relapse

FRNS Versus IFRNS		
Author, Year	**Risk Factor**	**Reported/Calculated Summary Statistics (95% Confidence Interval)**
Cetin et al. 2019 [15]	Age	OR=0.49 (0.14-1.69)
	Gender	OR=0.30 (0.06-1.47)
	Duration of treatment (months)	OR=308.93 (47.99-1988.82)
	Number of relapses	OR=53536.95 (28.4622, 1×10^{6})
Fan et al. 2015 [16]	Age	OR=0.23 (0.05-1.05)
	Gender	OR=0.50 (0.08-3.08)
	Serum albumin	OR=1.04 (0.24-4.47)
	Serum cholesterol	OR=1.11 (0.26-4.79)
	Mean arterial pressure	OR=0.83 (0.19-3.58)
Ali et al. 2016 [8]	Age 1-5 years	OR=0.69 (0.27-1.74)
	Age 5-10 years	OR=1.30 (0.49-3.50)
	Age >10 years	OR=1.61 (0.28-9.34)
	Gender	OR=0.38 (0.14-1.04)
	Hematuria	OR=6.70 (1.40-32.09)
	Serum creatinine elevation	OR=1.58 (0.14-18.18)
	Duration of treatment ≤2 month	OR=1.44 (0.54-3.85)
	Duration of treatment 2-3 month	OR=1.45 (0.57-3.69)
	Duration of treatment 3-6 month	OR=0.48 (0.19-1.24)
	Time to response 2 weeks	OR=0.05 (0.01-0.25)
	Time to response 2-4 weeks	OR=17.25 (3.69-80.65)
	Time to response 4-8 weeks	OR=2.39 (0.09-60.55)
Kabuki et al. 1998 [17]	Age	OR=1.00 (0.35-2.84)
	Gender	OR=0.89 (0.24-3.37)
	Number of relapses	OR=9.03 (2.55-31.94)
Nakanishi et al. 2013 [18]	Age	HR=1.5 (0.71-3.39)
	Gender	HR=1.41 (0.64-3.34)
	Serum albumin	OR=0.0001 (0.00-0.0001)
	Total protein	OR=28685.66 (5260.27, 1.6×10^{5})
	Serum cholesterol	HR=0.93 (0.74-1.18)
	Time to response (days)	HR=3.09 (1.42-7.27)
	Time to first relapse (<6 months to >6 months)	HR=2.06×10^{6} ($16.56-2.06\times10^{184}$)

FRNS Versus IFRNS		
Author, Year	**Risk Factor**	**Reported/Calculated Summary Statistics (95% Confidence Interval)**
Noer, 2005 [9]	Age ≤6	OR=1.45 (0.21-9.98)
	Gender	OR=0.75 (0.14-3.94)
	Hypertension	OR=32.67 (2.85-374.13)
	Hematuria	OR=3.50 (0.27-44.95)
	Time to response (>4 weeks vs <2 weeks)	OR=6 (1.01-35.91)
Zhaoyang et al. 2023 [10]	Age	OR=0.96 (0.30-3.12)
	Gender	OR=0.70 (0.17-2.99)
	Serum creatinine	OR=1.07 (0.33-3.48)
	Urine 24 h protein (mg/24 h)	OR=1.00 (0.31-3.23)
	Hypertension	OR=4.44 (0.37-54.00)

Relapse Versus No-relapse		
Author, Year	**Risk Factor**	**Reported/Calculated Summary Statistics (95% Confidence Interval)**
Bakr et al. 2009 [7]	Age	OR=0.74 (0.19-2.91)
	Gender	OR=2.25 (0.35-14.61)
	Serum Albumin	OR=0.33 (0.08-1.34)
	Serum creatinine	OR=1.23 (0.31, 4.80)
	Systolic blood pressure	OR=0.72 (0.18-2.82)
	Diastolic blood pressure	OR=1.68 (0.43-6.63)
	Urine 24 h protein (g/m^2/day)	OR=0.44 (0.11-1.75)
	Serum cholesterol	OR=2.33 (0.58-9.27)
Esezebor et al. 2016 [19]	Age	OR=0.89 (0.73-1.1)
	Gender	OR=0.41 (0.09-1.88)
	Serum creatinine	OR=1.00 (0.37-2.69)
	Hypertension	OR=0.78 (0.15-4.00)
	Hematuria	OR=1.04 (0.21-5.23)
Mishra et al. 2013 [6]	Age 1-3 years	HR=2.99 (1.573-5.68)
	Age 4-6 years	HR=1.624 (0.832-3.169)
	Age 7-13 years	Reference
	Gender	HR=1.13 (0.642-1.989)
	Hematuria	HR=1.56 (0.09-1.23)
	Hypertension	OR=0.77 (0.38-1.60)
	Infection at first relapse	OR=137.78 (18.15-1046.16)
	Time to response (1-2 weeks); ref: >4 weeks	HR=0.423 (0.201-0.89)
	Time to response (3-4 weeks); ref: >4 weeks	HR=0.584 (0.278-1.227)
	Serum Chol >350 (mg/dL)	OR=0.78 (0.39-1.58)
	Albumin >1.5 (g/dL)	OR=0.97 (0.37-2.53)
Takeda et al. 1996 [20]	Age	HR=2.28 (1.12-4.66)
	Total protein	HR=2.71 (1.27-5.78)

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Abbreviations: FRNS: Frequently relapsing nephrotic syndrome; IFRNS: Infrequently relapsing nephrotic syndrome; OR: Odds ratio; HR: Hazard ratio.

Table 3. Risk of bias assessment of cohort and cross-sectional studies

	Author, Year	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Overall
FRNS Versus IFRNS	Cetin et al. 2019 [15]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	NR	Yes	Yes	Fair
	Fan et al. 2015 [16]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	NR	Yes	Yes	Fair
	Ali et al. 2016 [8]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	NR	Yes	Yes	Fair
	Kabuki et al. 1998 [17]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	NR	Yes	Yes	Fair
	Nakanishi et al. 2013 [18]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	NR	Yes	Yes	Fair
	Noer, 2005 [9]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	NR	Yes	Yes	Fair
	Zhaoyang et al. 2023 [10]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	NR	Yes	Yes	Fair
Relapse Versus No-relapse	Bakr et al. 2009 [7]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	NR	Yes	Yes	Fair
	Esezobor et al. 2016 [19]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	NR	Yes	Yes	Fair
	Mishra et al. 2013 [6]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	NR	Yes	Yes	Fair
	Takeda et al. 1996 [20]	Yes	Yes	Yes	Yes	No	Yes	Yes	No	Yes	Yes	Yes	NR	Yes	Yes	Fair

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Abbreviations: FRNS: Frequently relapsing nephrotic syndrome; IFRNS: Infrequently relapsing nephrotic syndrome; NR: Not reported.

Notes: "Yes" shows low risk while "No" demonstrates high risk.

Items:

Item 1. Was the research question or objective in this paper clearly stated?

Item 2. Was the study population clearly specified and defined?

Item 3. Was the participation rate of eligible persons at least 50%?

Item 4. Were all the subjects selected or recruited from the same or similar populations (including the same period)? Were inclusion and exclusion criteria for being in the study prespecified and applied uniformly to all participants?

Item 5. Was a sample size justification, power description, or variance and effect estimates provided?

Item 6. For the analyses in this paper, were the exposure(s) of interest measured before the outcome(s) being measured?

Item 7. Was the timeframe sufficient so that one could reasonably expect to see an association between exposure and outcome if it existed?

Item 8. For exposures that can vary in amount or level, did the study examine different levels of the exposure as related to the outcome (e.g. categories of exposure, or exposure measured as a continuous variable)?

Item 9. Were the exposure measures (independent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?

Item 10. Was the exposure(s) assessed more than once over time?

Item 11. Were the outcome measures (dependent variables) clearly defined, valid, reliable, and implemented consistently across all study participants?

Item 12. Were the outcome assessors blinded to the exposure status of participants?

Item 13. Was the loss to follow-up after baseline 20% or less?

Item 14. Were key potential confounding variables measured and adjusted statistically for their impact on the relationship between exposure(s) and outcome(s)?

reported that time to first relapse can be a risk factor for frequent relapse (HR=2.09×10^6;

95% CI, 16.56%, 2.06%×10^{184}). Cetin et al. [15] and Kabuki et al. [17] demonstrated that the number of relapses could be a risk factor for frequent relapse (OR=53536.95 and 9.03, respectively).

Relapse versus no-relapse

Four articles (274 patients, 43.8% of patients experienced relapse) evaluated risk factors of relapse (Table 2). Mishra et al. [6] demonstrated that ages between 1-3 years had a higher risk of relapse (HR=2.99; 95% CI, 1.57%, 5.68%). In studies done by Bakr et al. [7] and Es-

Table 4. Certainty of evidence

Exposure		Sample Size (% Outcome)	Risk of Bias	Heterogeneity	Indirectness	Imprecision	Publication Bias	Quality of Evidence
FRNS Versus IFRNS	Age	449(30.73)	Not serious	Serious	Not serious	Serious	Not determined	Low to very low
	Gender	449(30.73)	Not serious	Serious	Not serious	Serious	Not determined	Low to very low
Relapse Versus No-relapse	Age	274(43.8)	Not serious	Serious	Not serious	Serious	Not determined	Low to very low
	Gender	274(43.8)	Not serious	Serious	Not serious	Serious	Not determined	Low to very low

FRNS: Frequently relapsing nephrotic syndrome; IFRNS: Infrequently relapsing nephrotic syndrome. Journal of Pediatrics Review

ezobor et al. [19], age was not a risk factor for relapse. Gender, hematuria at debut, blood pressure, serum creatinine, albumin, cholesterol at debut, and urine 24 h protein were not shown to be a risk factor for relapse. Mishra et al. [6] reported that patients with a median time from treatment to response between 1-2 weeks had a lower risk of relapse (HR=0.42; 95% CI, 0.20%, 0.89%, reference: >4 weeks). In their study, infection at first relapse was shown to be a risk factor for relapse. However, infection at presentation was not shown to be a risk factor [6].

Risk of bias assessment

The NHLBI protocol was employed to assess the quality of included studies (Table 3). Fatal items for this study were considered as follows: 3, 4, 6, 7, 9, 11, 13, and 14 of the NHLBI checklist (Table 3). None of the included studies had concerns about fatal items. All the studies showed a high risk of bias in items 5, 8, and 14, concerning the sample size justification, power description, variance and effect estimation, and examination of different levels of exposure. None of the studies reported the blinding status of the outcome assessment (item 12); therefore, they had a high risk of bias regarding this matter. Studies had a low risk of bias in the remaining items.

Certainty of evidence

According to the grading of recommendations, assessment, development, and evaluation guidelines, the base level of evidence is set as low for observational studies. The level of evidence was reduced due to high heterogeneity between study designs and due to imprecision (widely reported CIs), and thus the level of evidence is low to very low for age and gender (Table 4). However, according to Centre for Evidence-Based Medicine recommendations, systematic reviews of observational studies should have a base evidence level of high [21]. Accordingly, the level of evidence of this study can be presented as low to moderate for outcomes of age and gender. Certainty of evidence could not be assessed for other variables due to the scarcity of included articles and is rated as very low.

Discussion

The present study was designed to evaluate the risk factors of relapse in children and adolescents with SSNS. Our results demonstrated that some studies proposed age, hematuria, hypertension, longer duration of treatment, longer time from treatment to response, and shorter time to first relapse as possible risk factors of relapse. While other studies did not confirm these findings. None of the reported laboratory variables, such as serum creatinine, albumin, and cholesterol, were a risk factor for relapse. Several relapses and time from treatment to response seem to be risk factors for frequent relapse, albeit a scarce number of studies have investigated these factors.

Mishra et al. [6] compared relapsers to non-relapsers and reported that children between 1 and 3 years old had a higher risk of relapse, while Bakr et al. [7] and Esezobor et al. [19] did not report similar findings for age as a continuous variable. Patients with lower age groups might have a higher risk of relapse while older patients are not at risk. Meanwhile, studies investigating FRNS vs IFRNS did not demonstrate a value for age as a risk factor [10, 15-18] even in lower age groups (ages between 1 to 5) [8].

The risk factor value of various laboratory variables at debut (such as serum creatinine, serum albumin, serum cholesterol, and serum protein) was evaluated, and none of the studies reported a relation between these values and relapse in SSNS patients. However, the scarce number of studies and their heterogeneity should be considered.

Studies have also investigated disease-specific variables, such as time from treatment to response, duration of treatment, and number of relapses. Accordingly, a longer time to respond and a higher number of re-

lapses can be risk factors for relapse. The two studies with reports of the duration of treatment have shown conflicting results for its value in the prediction of relapse [8, 15]. Studies had different follow-ups which greatly affects the value of several relapses. The number of relapses per year could be a more concrete factor to investigate in future studies.

Conclusion

The present study aimed to evaluate possible risk factors for relapse of SSNS in children and adolescents. Low to very low evidence suggests that although factors such as hematuria, hypertension, time from treatment to response, and number of relapses have been proposed as possible risk factors of relapse, no conclusion can be reached due to the heterogeneity of studies. Future studies should have more conforming designs to make comparisons more reliable.

Study limitations

This study faced some limitations. Primarily, the included studies had reported various factors with differing comparison groups, making an overall conclusion difficult. We suggest that future studies be designed with attention to the current reported factors. The wide confidence interval reported for a few of the risk factors is also a limitation. Additionally, studies had variations in definitions of nephrotic syndrome, SSNS, relapse, frequent relapse, and their treatment regimens. Although the variations were minimal, they could still act as confounders. We suggest future studies conform more precisely to a uniform guideline.

Ethical Considerations

Compliance with ethical guidelines

The study was approved by the Ethics Committee of Tehran University of Medical Sciences (TUMS) (Code: IR.TUMS.CHMC.REC.1397.033).

Funding

This study has been funded and supported by Tehran University of Medical Sciences (Grant No.: 96-03-184-36538).

Authors contributions

Conceptualization and supervision: Mostafa Hosseini and Mahmoud Yousefifard; Methodology: Mostafa Hosseini, Mahmoud Yousefifard, Mohammed I M Gubari, Michael E. Jones, Nematollah Ataei and Mojtaba Fazel; Investigation and data curation: Arian Madani Neishaboori, Seyedeh Niloufar Rafiei Alavi, Koohyar Ahmadzadeh, Seyed Romina Rafiei Alavi, Hooman Ahmadzadeh and Amirmohammad Toloui; Formal analysis and validation: Mahmoud Yousefifard, Koohyar Ahmadzadeh and Mostafa Hosseini; Writing: All Authors.

Conflicts of interest

The authors declared no conflict of interest.

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Supplementary Material 1. Search strategy

Database	Search Terms
MEDLINE (PubMed)	"Prognosis" [mh] OR "risk factors"[mh] OR "sensitivity and specificity" [mh] OR "area under curve" [mh] OR "injury severity score" [mh] OR "biomarkers" [mh] OR "prognoses"[tiab] OR "prognostic factors"[tiab] OR "factor, prognostic"[tiab] OR "factors, prognostic"[tiab] OR "prognostic factor"[tiab] OR "factor, risk"[tiab] OR "risk factor"[tiab] OR "risk scores"[tiab] OR "risk score"[tiab] OR "score, risk"[tiab] OR "risk factor scores"[tiab] OR "risk factor score"[tiab] OR "score, risk factor"[tiab] OR "population at risk"[tiab] OR "populations at risk"[tiab] OR "prediction"[tiab] OR "specificity and sensitivity"[tiab] OR "sensitivity"[tiab] OR "specificity"[tiab] OR "area under curves"[tiab] OR "curve, area under"[tiab] OR "curves, area under"[tiab] Or "under curve, area"[tiab] OR "under curves, area"[tiab] OR "AUC"[tiab] OR "injury severity scores"[tiab] OR "score, injury severity"[tiab] OR "injury severity scores"[tiab] OR "score, injury severity"[tiab] OR "scores, injury severity"[tiab] OR "ISS score"[tiab] OR "injury scale"[tiab] OR "marker, biological"[tiab] OR "biological marker"[tiab] OR "biologic marker"[tiab] OR "marker, biologic"[tiab] OR "biological markers"[tiab] OR "biologic markers"[tiab] OR "markers, biologic"[tiab] OR "biomarker"[tiab] OR "markers, biological"[tiab] OR "markers, immunologic"[tiab] OR "immune markers"[tiab] Or "markers, immune"[tiab] OR "marker, immunologic"[tiab] OR "immunologic markers"[tiab] OR "immune marker"[tiab] OR "marker, immune"[tiab] OR "immunologic marker"[tiab] OR "serum markers"[tiab] OR "markers, serum"[tiab] OR "marker, serum"[tiab] OR "serum marker"[tiab] OR "surrogate endpoints"[tiab] OR "endpoints"[tiab] "steroid sensitive"[tiab] "Nephrotic syndrome" [mh] OR "nephrotic syndromes" [tiab] OR "syndrome, nephrotic" [tiab] OR "syndromes, nephrotic" [tiab] OR "edema hypertension proteinuria syndrome "[tiab] OR "epstein syndrome" [tiab] OR "idiopathic nephrotic syndrome" [tiab] OR "oedema hypertension proteinuria syndrome" [tiab] "Child"[mh] OR " infant"[mh] OR "adolescent"[mh] OR "child, preschool"[mh] OR "pediatrics"[mh] OR "young adult"[mh] OR "[mh] children"[tiab] OR "child"[tiab] OR "Infant"[tiab] OR "Juvenile"[tiab] OR "adolescent"[tiab] OR "infants"[tiab] OR "baby"[tiab] OR "newborn"[tiab] OR "adolescents"[tiab] OR "adolescence"[tiab] OR "teens"[tiab] OR "teen"[tiab] OR "teenagers"[tiab] OR "teenager"[tiab] OR "youth"[tiab] OR "youths"[tiab] OR "preschool child"[tiab] OR "children, preschool"[tiab] OR "preschool children"[tiab] OR "hospitalized infant"[tiab] OR "hospitalised infant"[tiab] OR "pediatric patients"[tiab] OR "juvenile"[tiab] OR "youth"[tiab] OR "adult, young"[tiab] OR "adults, young"[tiab] OR "young adults"[tiab] #1 AND #2 AND #3 AND #4

Database	Search terms
Embase	'Prognosis'/exp OR 'risk factor'/exp OR 'sensitivity and specificity'/exp OR 'area under the curve'/exp OR 'injury scale'/exp OR 'biological marker'/exp OR 'Prognosis':ab,ti OR 'risk factors':ab,ti OR 'sensitivity and specificity':ab,ti OR 'area under curve':ab,ti OR 'injury severity score':ab,ti OR 'biomarkers': ab, ti OR 'prognoses':ab,ti OR 'prognostic factors':ab,ti OR 'factor, prognostic':ab,ti OR 'factors, prognostic':ab,ti OR 'prognostic factor':ab,ti OR 'factor, risk':ab,ti OR 'risk factor':ab,ti OR 'risk scores':ab,ti OR 'risk score':ab,ti OR 'score, risk':ab,ti OR 'risk factor scores':ab,ti OR 'risk factor score':ab,ti OR 'score, risk factor':ab,ti OR 'population at Risk':ab,ti OR 'populations at risk':ab,ti OR 'prediction':ab,ti OR 'specificity and sensitivity':ab,ti OR 'sensitivity':ab,ti OR 'specificity':ab,ti OR 'area under curves':ab,ti OR 'curve, area m':ab,ti OR 'Curves, area under':ab,ti OR 'under curve, area':ab,ti OR 'under curves, area':ab,ti OR 'AUC':ab,ti OR 'injury severity scores':ab,ti OR 'score, injury severity':ab,ti OR 'injury severity scores':ab,ti OR 'score, injury severity':ab,ti OR 'scores, injury severity':ab,ti OR 'ISS score':ab,ti OR 'injury scale':ab,ti OR 'marker, biological':ab,ti OR 'biological marker':ab,ti OR 'biologic marker':ab,ti OR 'marker, biologic':ab,ti OR 'biological markers':ab,ti OR 'biologic markers':ab,ti OR 'markers, biologic':ab,ti OR 'biomarker': ab, ti OR 'markers, biological':ab,ti OR 'markers, immunologic':ab,ti OR 'immune markers':ab,ti OR 'markers, immune':ab,ti OR 'marker, immunologic':ab,ti OR 'immunologic markers':ab,ti OR 'immune marker':ab,ti OR 'marker, immune':ab,ti OR 'immunologic marker':ab,ti OR 'serum markers':ab,ti Or 'markers, serum':ab,ti OR 'marker, serum':ab,ti OR 'Serum marker': ab,ti OR 'surrogate endpoints':ab,ti OR 'endpoints':ab,ti 'steroid sensitive':ab,ti 'nephrotic syndrome'/exp OR 'nephrotic syndrome':ab,ti OR 'nephrotic syndromes':ab,ti OR 'syndrome, nephrotic':ab,ti OR 'syndromes, nephrotic':ab,ti OR 'edema hypertension proteinuria syndrome' OR 'epstein syndrome':ab,ti OR 'idiopathic nephrotic syndrome':ab,ti OR 'oedema hypertension proteinuria syndrome':ab,ti 'child'/exp OR 'infant'/exp OR 'Juvenile'/exp OR 'adolescent'/exp OR child':ab,ti OR 'infant':ab,ti OR 'adolescent':ab,ti OR 'child, preschool':ab,ti OR 'pediatrics':ab,ti OR 'young adult':ab,ti OR 'children':ab,ti OR 'child':ab,ti OR 'infant':ab,ti OR 'juvenile':ab,ti OR 'adolescent':ab,ti OR 'infants':ab,ti OR 'baby':ab,ti OR 'newborn':ab,ti OR 'adolescents':ab,ti OR 'adolescence':ab,ti OR 'teens':ab,ti OR 'teen':ab,ti OR 'teenagers':ab,ti OR 'teenager':ab,ti OR 'youth':ab,ti OR 'youths':ab,ti OR 'preschool child':ab,ti OR 'children, preschool':ab,ti OR 'preschool children':ab,ti OR 'hospitalized infant':ab,ti OR 'hospitalised infant':ab,ti OR 'pediatric patients':ab,ti OR 'juvenile':ab,ti OR 'youth':ab,ti OR 'adult, young':ab,ti OR 'adults, young':ab,ti OR 'young adults':ab,ti #1 AND #2 AND #3 AND #4

Database	Search Terms
Scopus	TITLE-ABS-KEY (“prognoses”) OR TITLE-ABS-KEY (“prognostic factors”) OR TITLE-ABS-KEY (“factor, prognostic”) OR TITLE-ABS-KEY (“factors, prognostic”) OR TITLE-ABS-KEY (“prognostic factor”) OR TITLE-ABS-KEY (“factor, risk”) OR TITLE-ABS-KEY (“risk factor”) OR TITLE-ABS-KEY (“risk scores”) OR TITLE-ABS-KEY (“risk score”) OR TITLE-ABS-KEY (“score, risk”) OR TITLE-ABS-KEY (“risk factor scores”) OR TITLE-ABS-KEY (“risk factor score”) OR TITLE-ABS-KEY (“score, risk factor”) OR TITLE-ABS-KEY (“population at risk”) OR TITLE-ABS-KEY (“populations at risk”) OR TITLE-ABS-KEY (“prediction”) OR TITLE-ABS-KEY (“specificity and sensitivity”) OR TITLE-ABS-KEY (“sensitivity”) OR TITLE-ABS-KEY (“specificity”) OR TITLE-ABS-KEY (“area under curves”) OR TITLE-ABS-KEY (“curve, area under”) OR TITLE-ABS-KEY (“curves, area under”) OR TITLE-ABS-KEY (“under curve, area”) OR TITLE-ABS-KEY (“under curves, area”) OR TITLE-ABS-KEY (“AUC”) OR TITLE-ABS-KEY (“injury severity scores”) OR TITLE-ABS-KEY (“score, injury severity”) OR TITLE-ABS-KEY (“injury severity scores”) OR TITLE-ABS-KEY (“score, injury severity”) OR TITLE-ABS-KEY (“scores, injury severity”) OR TITLE-ABS-KEY (“ISS score”) OR TITLE-ABS-KEY (“injury scale”) OR TITLE-ABS-KEY (“marker, biological”) OR TITLE-ABS-KEY (“biological marker”) OR TITLE-ABS-KEY (“biologic marker”) OR TITLE-ABS-KEY (“marker, biologic”) OR TITLE-ABS-KEY (“biological markers”) OR TITLE-ABS-KEY (“biologic markers”) OR TITLE-ABS-KEY (“markers, biologic”) OR TITLE-ABS-KEY (“biomarker”) OR TITLE-ABS-KEY (“markers, biological”) OR TITLE-ABS-KEY (“markers, immunologic”) OR TITLE-ABS-KEY (“immune markers”) OR TITLE-ABS-KEY (“markers, immune”) OR TITLE-ABS-KEY (“marker, immunologic”) OR TITLE-ABS-KEY (“immunologic markers”) OR TITLE-ABS-KEY (“immune marker”) OR TITLE-ABS-KEY (“marker, immune”) OR TITLE-ABS-KEY (“immunologic marker”) OR TITLE-ABS-KEY (“serum markers”) OR TITLE-ABS-KEY (“markers, serum”) OR TITLE-ABS-KEY (“marker, serum”) OR TITLE-ABS-KEY (“serum marker”) OR TITLE-ABS-KEY (“surrogate endpoints”) OR TITLE-ABS-KEY (“endpoints”) TITLE-ABS-KEY (“steroid sensitive”) TITLE-ABS-KEY (“nephrotic syndromes”) OR TITLE-ABS-KEY (“syndrome, nephrotic”) OR TITLE-ABS-KEY (“syndromes, nephrotic”) OR TITLE-ABS-KEY (“edema hypertension proteinuria syndrome “) OR TITLE-ABS-KEY (“epstein syndrome”) OR TITLE-ABS-KEY (“idiopathic nephrotic syndrome”) OR TITLE-ABS-KEY (“oedema hypertension proteinuria syndrome”) TITLE-ABS-KEY (“child”) OR TITLE-ABS-KEY (“Infant”) OR TITLE-ABS-KEY (“juvenile”) OR TITLE-ABS-KEY (“adolescent”) OR TITLE-ABS-KEY (“infants”) OR TITLE-ABS-KEY (“Baby”) OR TITLE-ABS-KEY (“newborn”) OR TITLE-ABS-KEY (“adolescents”) OR TITLE-ABS-KEY (“adolescence”) OR TITLE-ABS-KEY (“teens”) OR TITLE-ABS-KEY (“teen”) OR TITLE-ABS-KEY (“teenagers”) OR TITLE-ABS-KEY (“teenager”) OR TITLE-ABS-KEY (“youth”) OR TITLE-ABS-KEY (“youths”) OR TITLE-ABS-KEY (“preschool child”) OR TITLE-ABS-KEY (“children, preschool”) OR TITLE-ABS-KEY (“preschool children”) OR TITLE-ABS-KEY (“hospitalized infant”) OR TITLE-ABS-KEY (“hospitalised infant”) OR TITLE-ABS-KEY (“pediatric patients”) OR TITLE-ABS-KEY (“juvenile”) OR TITLE-ABS-KEY (“youth”) OR TITLE-ABS-KEY (“adult, young”) OR TITLE-ABS-KEY (“adults, young”) OR TITLE-ABS-KEY (“young adults”) #1 AND #2 AND #3 AND #4

Database	Search Terms
Web of Science	TS= (“prognoses” OR “prognostic factors” OR “factor, prognostic” OR “factors, prognostic” OR “prognostic factor” OR “factor, risk” OR “risk factor” OR “risk scores” OR “risk score” OR “score, risk” OR “risk factor scores” OR “risk factor score” OR “score, risk factor” OR “population at risk” OR “populations at risk” OR “prediction” OR “specificity and sensitivity” OR “sensitivity” OR “specificity” OR “area under curves” OR “curve, area under” OR “curves, area under” OR “under curve, area” OR “under curves, area” OR “AUC” OR “injury severity scores” OR “score, injury severity” OR “injury severity scores” OR “score, injury severity” OR “scores, injury severity” OR “ISS score” OR “injury scale” OR “marker, biological” OR “biological marker” OR “biologic marker” OR “marker, biologic” OR “biological markers” OR “biologic markers” OR “markers, biologic” OR “biomarker” OR “markers, biological” OR “markers, immunologic” OR “immune markers” OR “markers, immune” OR “marker, immunologic” OR “immunologic markers” OR “immune marker” OR “marker, immune” OR “immunologic marker” OR “serum markers” OR “markers, Serum” OR “marker, serum” OR “serum marker” OR “surrogate endpoints” OR “endpoints”) TS=(“steroid sensitive”) TS=(“nephrotic syndromes” OR “syndrome, nephrotic” OR “syndromes, nephrotic” OR “edema hypertension proteinuria syndrome “ OR “epstein syndrome” OR “idiopathic nephrotic syndrome” OR “oedema hypertension proteinuria syndrome”) #1 AND #2 AND #3

Supplementary Table 1. Definitions

FRNS vs IFRNS					
Author, Year	**Definition of Nephrotic Syndrome**	**Definition of Steroid Sensitive NS**	**Definition of Relapse**	**Frequent Relapse Definition**	**Patient Treatment Plan**
Cetin, 2019 [15]	KDIGO definition Massive proteinuria (3 + dipstick proteinuria or urinary protein >40 mg/m²/h, urine protein: Creatinine ratio>2 g/g) Hypoalbuminemia (serum albumin ≤2.5 g/dL) Edema	Remission during 8 weeks of steroid therapy	NR	≥2 in 1st 6 months or ≥4 in a period of 12 months	NR
Fan, 2015 [16]	Heavy proteinuria (dipstick 3+/4+, a random or morning urine protein/creatinine ratio (mg/mg) ≥2.0, or 24-h urinary protein ≥50 mg/kg, repeated three times in one week) Hypoalbuminemia (serum albumin <25 g/L) Hyperlipidemia (serum cholesterol >5.7 mmol/L) Edema Exclusion of secondary and congenital nephrotic syndrome	Negative protein on urine dipstick testing after induction therapy	Proteinuria (3+/4+) or 24-h urinary protein ≥50 mg/kg, or urine protein/creatinine ratio (mg/mg) ≥2.0 for 3 consecutive days	≥2 in 1st 6 1st or ≥3 in a period of 12 months	Oral prednisone (2 mg/kg/day or 60 mg/(m²/day) for 4 weeks as induction therapy
Ali, 2016 [8]	Heavy proteinuria >40 mg/h/m² (for older children with collected 24 h urine); or protein/creatinine ratio >0.2 g/mmol, Albustix ≥3+ (for non-toilet-trained children or difficult collection of 24-h urine) Hypoalbuminemia <2.5 g/dL Edema Hyperlipidemia with total cholesterol of 170-200 mg/dL	Complete remission within 4 weeks of steroid therapy	NR	≥2 in 1st 6 months or ≥4 in a period of 12 months	Initial attack: Prednisone 60 mg/m²/day in divided doses for four weeks followed by 40 mg/m²/day in divided doses. Followed by alternate-day therapy for four more weeks, which was tapered thereafter. Relapse: Prednisone 60 mg/m²/day, continued for three days after the urine became protein free, followed by alternate-day prednisone 40 mg/m² for four weeks.
Kabuki, 1998 [17]	ISKDC protocol Heavy proteinuria (≥40 mg/m² per hour) as determined quantitatively on an overnight urine collection Hypoalbuminemia (≤2.5 g/dL) Absence of systemic disease or exposure to agents known to be associated with NS	Response within 8 weeks of prednisolone therapy	Proteinuria for more than 3 consecutive days	ISKDC criteria ≥2 relapses/6 months or ≥4 relapses/12 months	ISKDC protocol Initial therapy: 60 mg/m² per day of prednisolone (≤80 mg/day) for 4 weeks Relapse: 60 mg/m² per day of prednisolone until response, followed by 40 mg/m² per day in divided doses for 3 consecutive days per week for 4 weeks, with subsequent tapering.
Nakanishi, 2013 [18]	NR	Response within 8 weeks of prednisolone therapy	Proteinuria of >40 mg/h per m² (dipstick ≥2+) for 3 consecutive days,	≥2 in 1st 6 months or ≥4 in a period of 12 months	ISKDC protocol Initial therapy: 2 mg/kg per day prednisolone (maximum of 80 mg) in three divided doses for 4 weeks followed by 1.3 mg/kg per 2 days in a single dose for 4 weeks Relapse: 2 mg/kg per day prednisolone for 4 weeks followed by tapering to 2 mg/kg per 2 days in a single dose for 2 weeks, 1.0 mg/kg per 2 days for 2 weeks, and 0.5 mg/kg/2 days for 2 weeks
Noer, 2005 [9]	ISKDC protocol Urinary total protein >1 g/m²/day or urinary spot creatinine ratio of >200 mg/mmol) Hypoalbuminemia (serum albumin <2.5 g/dL) Hypercholesterolemia (serum cholesterol >250 mg/dL) Edema	Response within 4 weeks of steroid therapy	Proteinuria (urine albumin 3+ or more) for 3 consecutive days	≥2 in 1st 6 months or ≥4 in a period of 12 months	Indian pediatric nephrology protocol Initial therapy: 2 mg/kg per day prednisolone at a dose of (maximum 60 mg in single or divided doses) for 6 weeks, followed by 1.5 mg/kg (maximum 40 mg) as a single morning dose on alternate days for the next 6 weeks Relapse: 2 mg/kg/day Prednisolone (single or divided doses) until urine protein is trace or nil for three consecutive days. Subsequently, prednisolone is given in a single morning dose of 1.5 mg/kg on alternate days for 4 weeks

FRNS vs IFRNS					
Author, Year	**Definition of Nephrotic Syndrome**	**Definition of Steroid Sensitive NS**	**Definition of Relapse**	**Frequent Relapse Definition**	**Patient Treatment Plan**
Zhaoyang, 2023 [10]	24-h urinary protein excretion of ≥50 mg/ kg Morning urinary protein/creatinine of >2 mg Hypoalbuminemia of <25 g/L Edema Disease of unknown causing	Response within 4 weeks of steroid therapy	Urinary protein ≥50 mg/kg, or urinary protein/creatinine (mg/mg) of morning urine ≥2.0, or the morning urinary protein changed from negative to positive for three consecutive days	≥2 in 1st 6 months or ≥4 in a period of 12 months	Sufficient prednisone: 2 mg/kg/d or 60 mg/m/d
Relapse vs No Relapse					
Bakr, 2009 [7]	ISKDC criteria Heavy proteinuria, ≥40 mg/hour/m^2, determined quantitatively on an overnight collection Hypoalbuminemia, ≤2.5 g/dL Age >12 weeks and <16 years No prior treatment with steroids or other cytotoxic or immunosuppressive agents No evidence of underlying systemic disease or exposure to agents known to be associated with the nephrotic syndrome	Response to standard corticosteroid induction therapy	NR	NA	Standard oral corticosteroid induction therapy for one month
Esezebor, 2016 [19]	KDIGO criteria Massive proteinuria (3 + dipstick proteinuria or urinary protein >40 mg/m^2/h, urine protein: Creatinine ratio>2 g/g) Hypoalbuminemia (serum albumin ≤2.5 g/dL) Edema	NR	Proteinuria of atleast 3+ on dipstick for 3 consecutive days	NA	KDIGO criteria Initial therapy: oral prednisolone at a daily dose of 60 mg/m^2, (maximum dose, 60 mg) for 4 weeks. When remission was not achieved within 4 weeks prednisolone was continued for another 2 weeks. Prior to July 2010, the initial prednisolone dose for a day was given in divided doses. After attaining remission and receiving at least 4 weeks of prednisolone, the dose was reduced to 40 mg/m^2 (maximum dose, 40 mg), every other day for 4 weeks. Relapse: prednisolone at a daily dose of 60 mg/m^2 until remission. Thereafter, the dose of prednisolone was reduced to 40 mg/m^2 alternate day for 4 weeks. If the child remained in remission, prednisolone was tapered over 4 weeks
Mishra, 2013 (6)	Heavy proteinuria (>40 mg/m^2/h) Hypoalbuminemia (serum albumin, <2.5 mg/dL) Hypercholesterolemia (serum cholesterol >200 mg/dL) Generalized edema	Response within 8 weeks of steroid therapy	Proteinuria of >40 mg/m^2/h or urine albumin 3+ or more by heat precipitation test for 3 consecutive days,	NA	2 mg/kg/day prednisone, until remission, followed by 1.5 mg/kg on alternate days for 4 weeks
Takeda, 1996 [20]	NR	Response within 8 weeks of steroid therapy	Proteinuria ≥40 mg/h per m^2 (dipstick 2+ or greater) for 3 consecutive days	NA	60 mg/m^2 (maximum 80 mg) of prednisolone daily for 4 weeks, with the dose then tapered over a 5-month period

Journal of Pediatrics Review

Abbreviations: ISKDC: International study of kidney disease in children; KDIGO: Kidney disease: Improving global outcomes; NR: Not reported. NA: Not applicable.

Supplementary Table 1. Definitions

Supplementary Table 2. Raw data of the included articles

	Author, Year	Risk Factor	No.				Mean±SD	
			Risk Factor in Cases	Risk Factor in Control	No Risk Factor in Cases	No Risk Factor In Controls	Factor in Cases	Risk Factor in Control
FRNS vs IFRNS	Cetin, 2019 [15]	Age	---	---	---	---	3.5±1.13	4.09±1.73
		Gender	9	13	7	3	---	---
		Duration of treatment (months)	---	---	---	---	48.1±12.4	13.7±8.39
		Number of relapses	---	---	---	---	6.19±0.78	2±0.56
	Fan, 2015 [16]	Age	---	---	---	---	4.3±1.89	6.5±3.1
		Gender	6	9	4	3		
		Serum albumin	---	---	---	---	19.8±1.62	19.75±2.83
		Serum cholesterol	---	---	---	---	9.61±1.23	9.52±1.66
		Mean arterial pressure	---	---	---	---	77.4±7.01	78.25±8.57
	Ali et al. 2016 [8]	Age 1-5	27	24	18	11	---	---
		Age 5-10	14	9	31	26	---	---
		Age >10	4	2	41	33	---	---
		Gender	27	28	18	7	---	---
		Hematuria	13	2	32	33	---	---
		Serum Cr elevation	2	1	43	34	---	---
		Duration of treatment: ≤2 month	15	9	30	26	---	---
		Duration of treatment: 2-3 month	18	11	27	24	---	---
		Duration of treatment: 3-6 month	12	15	33	20	---	---
		Time to response: 2 w	21	33	24	2	---	---
		Time to response: 2-4 w	23	2	22	33	---	---
		Time to response: 4-8 w	1	0	44	35	---	---
	Kabuki, 1998 [17]	Age	--	--	--	--	5.1±2	5.1±2.4
		Gender	11	34	4	11	--	--
		Number of relapses	---	---	---	---	13.2±10.1	4.6±5.9
	Nakanishi, 2013 [18]	Age	---	---	---	---	4.83±3.96	5.73±5.02
		Gender	23	70	9	36	---	---
		Serum albumin	---	---	---	---	1.6±0.47	4.1±0.61
		Total protein	---	---	---	---	4±0.47	1.63±0.38
		Serum Chol	---	---	---	---	405.67±127.27	456±80.62
		Time to response (days)	---	---	---	---	10.33±3.88	7±1.5
		Time to 1st relapse (<6 months to >6 months)	---	---	---	---	2.53±1.55	--

	Author, Year	Risk Factor	No.				Mean±SD	
			Risk Factor in Cases	Risk Factor in Control	No Risk Factor in Cases	No Risk Factor In Controls	Factor in Cases	Risk Factor in Control
FRNS vs IFRNS	Noer, 2005 [9]	Age ≤6	8	11	2	4	---	---
		Gender	6	10	4	5	---	---
		Hypertension	7	1	3	14	---	---
		Hematuria	2	1	8	14	---	---
		Time to response (>4 w vs <2 w)	6	3	4	12	---	---
	Zhaoyang, 2023 [10]	Age	---	---	---	---	3.78±1.93	3.84±2.77
		Gender	7	63	3	19	---	---
		Serum Cr	---	---	---	---	39.9±3.99	39.4±13.7
		Urine 24 h Pr (mg/24 h)	---	---	---	---	2219.6±1277.4	2225.2±2242.8
		Hypertension	1	2	9	80	---	---
Relapse vs No relapse	Bakr, 2009 [7]	Age	---	---	---	---	4.3±2	4.7±2.8
		Gender	9	10	2	5		
		Serum albumin	---	---	---	---	1.7±0.33	1.9±0.3
		Serum Cr	---	---	---	---	0.7±0.27	0.67±0.24
		Systolic BP	---	---	---	---	95±4.47	96±6.32
		Diastolic BP	---	---	---	---	62.72±0.1	61.3±7.4
		Urine 24 h Pr ($g/m^2/day$)	---	---	---	---	3.22±0.97	3.6±0.5
		Serum Chol	---	---	---	---	352.18±16.73	346±1.9
	Esezebor, 2016 [19]	Age	---	---	---	---	5.75±3.58	6.3±2.35
		Gender	18	4	6	6	---	---
		Serum Cr	---	---	---	---	0.75±0.36	0.75±0.39
		Hypertension	6	3	18	7	---	---
		Hematuria	6	4	18	6	---	---

	Author, Year	Risk Factor	No.				Mean±SD	
			Risk Factor in Cases	Risk Factor in Control	No Risk Factor in Cases	No Risk Factor In Controls	Factor in Cases	Risk Factor in Control
Relapse vs No relapse	Mishra, 2013 [6]	Age 1-3	47	16	42	45	---	---
		Age 4-6	26	22	63	39	---	---
		Age 7-13	16	23	73	28	---	---
		Gender	64	44	25	17	---	---
		Hematuria	11	13	78	48	---	---
		Hypertension	61	45	28	16	---	---
		Infection at 1st relapse	62	1	27	60	---	---
		Time to response (1-2 weeks), Ref: >4 weeks	---	---	---	---	---	---
		Time to response (3-4 weeks) ref: >4 weeks	---	---	---	---	---	---
		Serum Chol >350 (mg/dL)	58	43	31	18	---	---
		Albumin >1.5 (g/dL)	77	53	12	8	---	---
	Takeda, 1996 [20]	Age	---	---	---	---	---	---
		Total protein	---	---	---	---	---	---
		Albumin infusions	---	---	---	---	---	---

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FRNS: Frequently relapsing nephrotic syndrome; IFRNS: Infrequently relapsing nephrotic syndrome; HR: Hazzard ratio; OR: Odds ratio

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