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Biomarkers Predicting Treatment-Response in Nephrotic Syndrome of Children: A Systematic Review

Jiwon M. Lee, M.D., Ph.D[1]
Yo Han Ahn, M.D., Ph.D[2,3]
Seon Hee Lim, M.D.[3]
Hee Gyung Kang, M.D., Ph.D.[2,3,4,5]

[1]Division of Rare Disease Management, Bureau of Chronic Disease Management, Korea Disease Control and Prevention Agency, Osong, Korea; [2]Department of Pediatrics, Seoul National University College of Medicine, Seoul, Korea [3]Department of Pediatrics, Seoul National University Children's Hospital, Seoul, Korea; [4]Kidney Research Institute, Medical Research Center, Seoul National University College of Medicine, Seoul, Korea; [5]Wide River Institute of Immunology, Seoul National University, Seoul, Korea

Corresponding author:
Hee Gyung Kang, M.D., Ph.D.
Division of Pediatric Nephrology
Department of Pediatrics Seoul National University College of Medicine 101 Daehak-ro, Jongno-gu, Seoul 03080, Korea
Tel: +82-2-2072-0658
Fax: +82-2-743-3455
E-mail: kanghg@snu.ac.kr

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Purpose: Nephrotic syndrome (NS) is the most common form of glomerulopathy in children. Most pediatric patients respond to glucocorticosteroid treatment (steroid-sensitive NS, SSNS), while approximately 10–15% will remain unresponsive or later become steroid-resistant. There has been a long-standing effort to find biomarkers that may predict steroid responsiveness.

Methods: We systematically reviewed current studies which investigated clinically relevant biomarkers for predicting steroid responsiveness in pediatric NS. We performed a PubMed and EMBASE search to identify eligible articles. We collected data on urinary markers, blood/serum markers (including cellular phenotypes and mRNA expression), genotypes and HLA allele frequency.

Results: A total of 659 articles were identified following electronic and manual searches. After reviewing the titles, abstracts, and full texts, 72 eligible articles were finally included. Vitamin D-binding protein (VDBP) seemed to be significantly elevated in SRNS than in SSNS, in both serum and urine specimen, although further validation is required.

Conclusions: The present paper narratively illustrates current understandings of potential biomarkers that may help predict steroid responsiveness. Further investigation and collaboration involving a larger number of patients are necessary.

Key words: Nephrotic syndrome, Steroid resistant, Biomarker, Treatment, Pediatric

Introduction

Nephrotic syndrome (NS), characterized by massive proteinuria and generalized edema, is the most common kidney glomerulopathy in children[1)]. Most pediatric patients respond to glucocorticosteroid treatment (steroid-sensitive NS, SSNS), with a good long-term prognosis, although multiple relapses are common[2,3)]. Since SSNS accounts for majority of pediatric cases, the first step in the management of NS in children is steroid trial, if secondary causes or contraindications of steroid treatment are not present[4)]. This strategy is different from NS in adults, where kidney biopsy is the first step[5)]. Nevertheless, some pediatric patients do not respond to steroid treatment (steroid-resistant NS, SRNS)[3)]. However, the initial presenting symptoms of SRNS do not differ from those of SSNS, and there are no widely accepted biomarkers that can predict steroid responsiveness, leading SRNS patients to unnecessary steroid exposure[6)]. In addition, some patients with SRNS respond to calcineurin inhibitors (CNIs), such as cyclosporine or tacrolimus, while

others are more responsive to mycophenolate mofetil (MMF) or rituximab and others may not respond to any immunosuppression[7,8]. The prognosis of SRNS is poor and approximately half of the patients progress to end-stage kidney disease (ESKD) within 10 years after initial presentation[9,10].

In addition, SRNS often recur after kidney transplantation except for certain cases with genetic etiology[9,11]. In general, recurrence of NS is often evident within 48 hours of re-vascularization of the allograft kidney, indicating the presence of circulating factors[12]. Of note, many patients who relapse with proteinuria after kidney transplantation respond to intensification of immunosuppression, including methylprednisolone pulse therapy, plasmapheresis, and rituximab[12,13]. Typically, these intensive treatments are applied within a few days of recurrence of NS. Considering that the same circulating factors likely have caused NS in the naïve kidneys[14,15], the responsiveness to immunosuppression in post-transplantation grafts may suggest that the poor treatment response in SRNS in the naïve kidneys may have been due to less effective treatment. Clearly, there are patients with genetic SRNS who would not theoretically respond to immunosuppression[8,16], in which case steroid treatment would only increase unnecessary side effects[17].

There has been a long-standing effort to find biomarkers that may predict steroid responsiveness in pediatric NS[6]. We systematically reviewed these efforts to identify clinically relevant biomarkers that may help differentiating SRNS and SSNS.

Materials and methods

1. Search strategy and data extraction

We performed a PubMed and EMBASE search to identify eligible articles. Furthermore, a forward search of the retrieved articles was performed. The last search was performed on August 27, 2020. The search terms were as follows: "(nephrotic syndrome OR nephrosis) AND (child* OR pediatric OR paediatric) AND (marker OR predict* OR differentiat*) AND (steroid* OR predniso*) AND resistan* AND (sensitive OR respond OR respons*). We examined and screened the articles first by the title, followed by the abstract, and finally by examining the full text. The detailed process of the article selection is shown in Fig. 1.

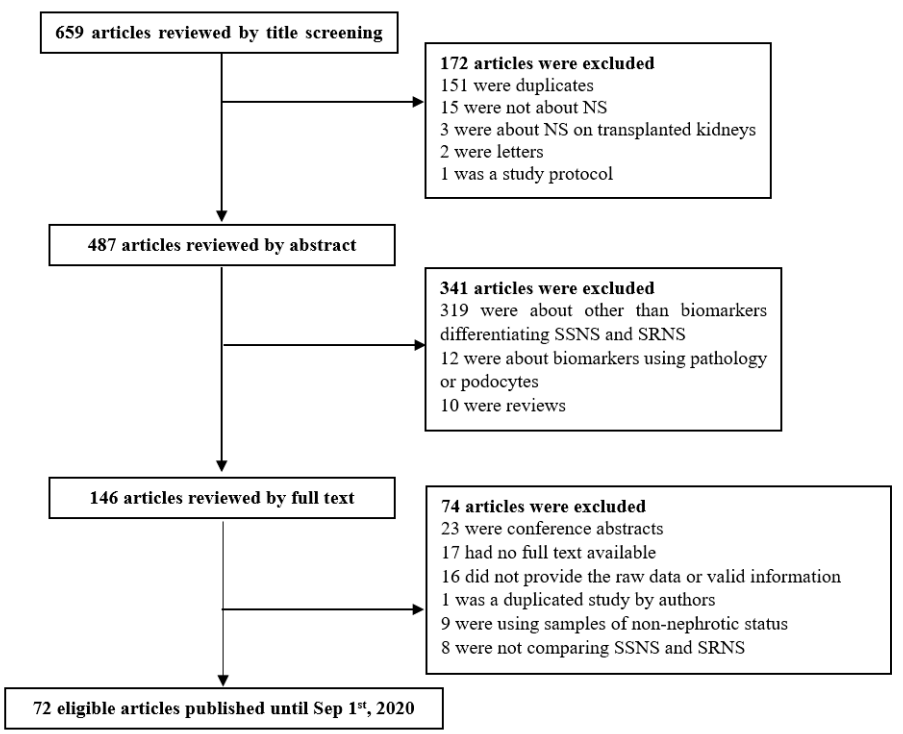

Fig. 1. Flow chart of literature search. NS, nephrotic syndrome; SSNS, steroid sensitive NS; SRNS, steroid resistant nephrotic syndrome.

Data were extracted from articles in which SSNS and SRNS were compared regarding candidate biomarkers. Demographic data, disease status (in relapse or at remission), medication, value of markers in the SSNS and SRNS groups, statistical significance, area under the receiver operating characteristic (ROC) curve (AUC), and cut-off values were collected. When the SSNS group included both cases of active or relapse and remission, data from active cases were archived. This report adhered to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines[18].

2. Selection of studies

Two reviewers (Jiwon M. Lee and Hee Gyung Kang) independently evaluated the potential eligibility of each abstract and title that resulted from the initial search. The full-text versions of eligible studies were then reviewed and discussed. Disagreements were resolved via consensus or, if not possible, through arbitration by a third reviewer (Yo Han Ahn).

3. Eligibility and exclusion criteria

Studies that compared SSNS and SRNS with data from the urine or blood specimens were included. Except for genotyping, clinical data obtained at active nephrotic state were and analyzed. Omics studies without validation or identified molecules were excluded. Biomarkers using pathologic findings or cell culture were excluded. Duplicates, letters, conference abstracts, commentaries, and replies were excluded. Articles that did not contain patient data such as review articles and those without explicit data were excluded[19-39].

4. Statistical analysis

Descriptive data are expressed as mean±standard deviation (SD), median (range), or interquartile range (IQR)[36,40] according to the expression of the source study. The 95% confidence intervals (CI) are denoted as < >. When original individual data were reported but no statistics were given, Mann–Whitney analysis was performed using SPSS (IBM SPSS Statistics for Windows, version 20; IBM Corp., Armonk, NY, USA). For meta-analysis, Cochrane Review Manager (version 5.4; Cochrane Library, UK) was used when necessary, using the random effects model as previously reported[41]. Data were converted when comparisons using the same units were necessary. Results are expressed as odds ratios (OR) and 95% CI for dichotomous data. Statistical significance was set at $P<0.05$.

5. Study selection and characteristics

A total of 659 articles were identified by electronic and manual searches. After reviewing the titles and abstracts, 146 studies were selected for full-text reading. Of them, 74 were excluded due to a lack of relevance or appropriateness (Fig. 1), leading to the final inclusion of 72 eligible articles. The investigated biomarkers were classified as urinary markers and peripheral blood markers. The peripheral blood markers included cellular phenotypes, serum or plasma markers, and mRNA expression. In addition, genetic polymorphisms and HLA allele freqeuncies were also analyzed.

Results

1. Urinary markers (Table 1)

1) Markers related to kidney damage

Molecules indicating tubular damage were evaluated as markers of the steroid treatment response. Urinary levels

Table 1. Urinary Markers

Marker	Method (unit)	No. of SSNS (M:F) Age	No. of SRNS (M:F) Age	Value in SSNS	Value in SRNS	*P* value	AUC <95% CI>	Cutoff	Author, year	Significant
A1BG[a]	ELISA (n.p.)	14 7.5±0.8	17 12.3±1.2	241.52 <97.01–601.29>	318.05 <139.00–727.74>	n.s.	0.58 <0.36–0.79>		Bennett, 2017	N
A2M/Cr	ELISA (μg/mg)	20 (15:5) 6.28±3.65	20 (16:4) 8.43±4.13	0.906 [0.07–43.61]	3.35 [0.01–10.32]	n.s.			Suresh, 2016	N
A2M[a]	Immunonephelometry (n.p.)	14 7.5±0.8	17 12.3±1.2	110.19 <31.70–383.10>	137.11 <44.26–424.79>	n.s.	0.52 <0.30–0.73>		Bennett, 2017	N
AAT[†]	ELISA (n.p.)	58 (43:15) 5±3	26 (18:8) 6±4	3.9 [[2.3-6.5]]	9.6 [[8.2–18.8]]	<0.05	0.899	0.0696	Yang, 2015	Y

Table 1. Continued

Marker	Method (unit)	No. of SSNS (M:F) Age	No. of SRNS (M:F) Age	Value in SSNS	Value in SRNS	*P* value	AUC <95% CI>	Cutoff	Author, year	Significant
AGP1[a]	ELISA (n.p.)	14 7.5±0.8	17 12.3±1.2	1340.72 <179.35–10 022.32>	141.97 <22.88–881.03>	n.s.	0.57 <0.35–0.79>		Bennett, 2017	N
AGP2 (ORM2)/Cr	ELISA (μg/mg)	20 (15:5) 6.28±3.65	20 (16:4) 8.43±4.13	3.23 [0.78–40.12]	2.47 [0.005–14.14]	n.s.			Suresh, 2016	N
AGP2 (ORM2)[a,b]	ELISA (n.p.)	14 7.5±0.8	17 12.3±1.2	266.72 <117.65–604.69>	171.01 <81.37–359.43>	n.s.	0.60 <0.39–0.80>		Bennett, 2017	N
24hr urine Annexin V	ELISA (ng/g)	23 (11:12) 9.4±3.4	22 (17:5) 9.2±4.5	5,048.8 [1,272.5–40,498.4]	2,839.5 [131.1–5,835.4]	0.006		≥4,000	Simsek, 2008	Y
APO A1/Cr	ELISA (μg/mg)	20 (15:5) 6.28±3.65	20 (16:4) 8.43±4.13	3.699 [0.484–56.17]	0.133 [0.05–0.29]	<0.001	0.99 <0.9-1.0>	SRNS <0.48	Suresh, 2016	Y
β2MG/Cr	Radioimmunoassay (μg/mM)	39	17	26.70	37.19	n.s.			Calişkan, 1996	N
CD80/Cr	ELISA (ng/g)	25 (21:4) 7.0 [[5.0, 8.5]]	30 (18:12) 4.5 [[3.0, 11.0]]	536.8 [[297.8,913.5]]	870.0 [[518.3,1186.4]]	0.029			Sinha, 2016	Y
Fetuin-A[a,b]	ELISA (n.p.)	14 7.5±0.8	17 12.3±1.2	15,607.72 <6,006.81–40,554.13>	36 723.78 <13,878.94–97,171.38>	n.s.	0.68 <0.48–0.88>		Bennett, 2017	Y
GAG/Cr	Dimethylmethylene blue assay (mg/g)	34 (21:13) 3.7±1.6	20 (12:8) 10.9±3.8	132.15±101.55	113.01±78.46	n.s.			Cengiz, 2005	Y
Hemopexin[a]	ELISA (n.p.)	14 7.5±0.8	17 12.3±1.2	3126.86 <1,120.64–8,724.72>	4019.45 <1583.99–10 199.55>	n.s.	0.56 <0.35–0.77>		Bennett, 2017	Y
LRG1/Cr	ELISA (μg/mg)	20 (15:5) 6.28±3.65	20 (16:4) 8.43±4.13	4.83 [1.25–30.98]	6.66 [0.69–83.96]	n.s.			Suresh, 2016	N
NAG/Cr (U/mM)	Enzyme assay (U/mM)	39	17	5.9.	4.09	n.s.			Calişkan, 1996	N
NAG/Cr[†]	(U/g)	27 (18:9) 4.6±3.05	8 (6:2) 6.19±4.9	99.8±24.18	167.5±63.6	<0.001	0.921 [0.832–1.011]	SSNS ≤108.9	Mishra, 2012	N
NGAL NGAL/Cr	ELISA (ng/mL, ng/mg)	9	15 (10:5)	6.3[[5.7–22.8]]	172.3 [[18.8–789]]	<0.001	0.91	15	Bennett, 2012	Y
NGAL/Cr	ELISA (ng/mg)	25 (18:7) 5.8±3.3	27 (16:11) 6.3±3.9	0.20 [0.10–0.32]	1.15 [0.15–11.36]	0.001	0.7593 < 0.6195–0.8990>	0.46	Nickavar, 2016	Y
NGAL[a,b]	ELISA (n.p.)	14 7.5±0.8	17 12.3±1.2	7.16 <3.00–17.06>	33.48 <15.22–73.64>	0.011	0.76 <0.58–0.94>		Bennett, 2017	Y
PBSA/Cr[†]	Aminoff's method (μg/mg)	47 (39:8) 5.82 ±1.1	23 (7:1) 6.30±0.8	2.10±0.73	3.92±1.24	<0.05	0.814	2.71	Gopal, 2016	Y
Prealbumin[a,b]	ELISA (n.p.)	14 7.5±0.8	17 12.3±1.2	5,000.48 <1,655.35–15,105.43>	33,079.70 <12,129.94–90,212.00>	0.014	0.73 <0.55–0.91>		Bennett, 2017	Y
RBP	ELISA (mg/L)	17	10	0.135 [0.022–6.645]	11.16[0.072-85.89]	0.001		>1.0	Mastroianni, 2000	Y
RBP4/Cr	ELISA	20 (15:5) 6.28±3.65	20 (16:4) 8.43±4.13	2.06 [0.49–31.33]	1.67 [0.003–10.68]	n.s.			Suresh, 2016	N
Thyroxine-binding globulin[a]	ELISA (n.p.)	14 7.5±0.8	17 12.3±1.2	1237.83 <275.92–5553.08>	1639.78 <419.97–6402.53>	n.s.	0.57 <0.36–0.78>		Bennett, 2017	N
VDBP	ELISA (ng/mL)	10	24 (Higher Cr) 11.3	203.7 [[39.7–717.9]]	13,659 [[477–22,979]]	0.007	0.87	362	Bennett, 2016	Y
VDBP[a,b]	ELISA (n.p.)	14 7.5±0.8	17 12.3±1.2	353.58 <84.36–1,482.06>	3708.40 <1010.16–13,613.90>	0.018	0.77 <0.58–0.96>		Bennett, 2017	Y
WT1 (exosomal)	(densitometry)	28	12	Detected in 60.7%, 2.48±1.62	Detected in 66.7%, 1.80±0.65	n.s.			Lee, 2012	N
MLM-10		14 7.5±0.8	17 12.3±1.2				0.92 <0.83–1.00>	0.6	Bennett, 2017	Y
MLM-5[b]		14 7.5±0.8	17 12.3±1.2				0.82 <0.66–0.99>	0.6	Bennett, 2017	Y

[†]at disease onset.

Abbreviations: SSNS, steroid-sensitive nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome; For values, [ ] for range, [[ ]] for interquartile range, < > for 95% confidence interval; A1BG, alpha-1 beta glycoprotein; n.p not provided; n.s,. not significant; A2M, α2 macroglobulin; Cr, creatinine; AAT, alpha 1-antitrypsin; AGP1, α1 acid glycoprotein 1; AGP2, α1 acid glycoprotein 2; ORM2, orosomucoid 2; APO A1, apolipoprotein A1; β2M, β2-microglobulin; GAG, glycosaminoglycans; LRG1, leucine-rich α2-glycoprotein 1; NAG, N-acetyl-beta-D-glucosaminidase; PBSA, protein bound sialic acid; RBP, retinol-binding protein; VDBP, vitamin D-binding protein; MLM-5[b] & MLM-10[a], panels of biomarkers[46].

of retinol-binding protein (RBP), an index of proximal tubular dysfunction, were higher in SRNS before steroid treatment, and urinary RBP ≥1.0 mg/L had an OR for SRNS of 30[47]. Urinary RBP4/Cr was later investigated and could not differentiate SSNS and SRNS, while a cutoff value of >1.54 μg/mg could differentiate FSGS from minimal change disease among cases of SRNS[46]. Annexin V (ANX5), an indicator of acute renal injury and apoptosis, was measured in 24-hr-urine specimen and found to be lower in SRNS, with a proposed cutoff value of ≥4,000 ng/g urinary creatinine for SSNS[48]. This finding was repeatedly supported by conference abstracts, reporting a cutoff value of 520.1 μg/mmol or 3.15 ng/mg urinary creatinine in the spot urine[25,28], but the full text was not published for these studies. Neutrophil gelatinase-associated lipocalin (NGAL), a well-known marker of damage in the kidney and is rapidly upregulated in cases of renal injury, was also increased in SRNS with an AUC of 0.91 and suggested a cutoff value of 15 ng/mg urinary Cr[49] or an AUC of 0.76 with a cutoff 0.46 ng/mg[50,51]. Urinary exosomal WT1, a potential biomarker of podocyte injury, was not different between the groups[52]. Urine levels of vitamin D–binding protein (VDBP), a potential indicator of renal interstitial damage[53], were higher in SRNS than in SSNS and was able to differentiate with an AUC of 0.87[54]. VDBP was also found to be a significant marker in a proteomics study[51].

2) Markers related to the pathogenesis of NS

The components of the charge-selective barrier of the glomerular basement membrane, glycosaminoglycan (GAG), and protein-bound sialic acid (PBSA) were investigated in the literature for their potential as biomarkers. While urinary GAG levels did not differ between SSNS and SRNS[55], PBSA was found to differentiate SRNS and SSNS with an AUC of 0.814 with a cutoff of 2.71 Cr[56]. Cytokines have been speculated to be involved in the pathogenesis of NS and increased protein permeability of the glomerular filtration barrier[57]. Increased urinary CD80 is considered pathogenic in NS and was tested in one study but was not indicative of steroid responsiveness[58].

3) Low-molecular weight proteins

Urine N-acetyl-beta-D-glucosaminidase and β2 microglobulin were evaluated[42-44] and found to be increased in SRNS in one previous study[44] but not in another[43]. No cut-off values were obtained.

4) Proteomics study

With advancements in technology, proteomics tools have become available for prognostic marker searches in NS. Proteomics studies in urine β2 microglobulin level showed contradicting results; significant in one study[42] but not supported in a more recent study which used modernized proteomics tools[45,46]. The former study detected β2 microglobulin (11.1 kDa) using surface-enhanced laser desorption/ionization time-of-flight mass spectrometry (SELDI-TOF MS)[42]. The latter study by Piyaphanee et al. also used SELDI-TOF MS and identified a 13.8-kDa α1-B glycoprotein (A1BG) fragment as a marker of SRNS[45], but expression of A1BG was found in only some patients with SRNS and those with lower eGFR. This molecule was evaluated independently by another study, but no statistically significant differences were found between SSNS and SRNS[51]. α1 antitrypsin was differentially expressed in a Chinese study and validated independently and was found to differentiate the two treatment response groups with an AUC of 0.899[40]. Later, isobaric tags for relative and absolute quantitation (iTRAQ) combined with multidimensional liquid chromatography (LC) and matrix-assisted laser desorption ionization-mass spectrometry/mass spectrometry, identified apolipoprotein A1 (APO A1, 28 kDa), α 2 macroglobulin (A2M, 720 kDa), orosomucoid 2 (α-1 acid glycoprotein 2, AGP2, 42 kDa), RBP 4 (21 kDa), and leucine-rich α 2-glycoprotein 1 (LRG1, 50 kDa) as differentially expressed proteins in SRNS compared to SSNS[46]; however, a validation study revealed that only APO A1 could differentiate SRNS and SSNS (cutoff for SRNS <0.4 μg/mg). A similar study using the iTRAQ method followed by nanoscale liquid chromatography coupled to tandem mass spectrometry (nanoLC-MS/MS) found VDBP (58 kDa), alpha-1 acid glycoprotein 1 (AGP1), AGP2, A1BG, fetuin-A, prealbumin, thyroxine-binding globulin, hemopexin, and A2M[51] were differentially expressed proteins, and their validation study revealed that prealbumin and VDBP levels were different between SSNS and SRNS. They also suggested using their models in 5 or 10 urinary markers to predict treatment response with an AUC >0.8.

2. Peripheral blood markers

1) Serum or plasma markers (Table 2)

(1) Immune reaction-related markers

IL-8 and soluble IL-2 receptor levels were higher in SRNS compared to SSNS[60,61]. Differences in immunoglobulin concentrations were found to be significant only in IgG and IgE, implying that these differences originate from the urinary loss of these proteins, rather than an aberration of immune function[62-64]. A low IgG/IgM ratio suggested SRNS with statistical significance (Fig. 2). Soluble tumor necrosis factor receptors (TNFR) were not predictive of responsiveness to treatment[59].

(2) Soluble urokinase-type plasminogen activator receptor (suPAR)

suPAR was once postulated to be the circulating permeability factor in FSGS or SRNS[65], but it was soon refuted by several studies[66,67]. Regarding predictive markers of steroid responsiveness in children with NS, two studies were found [68,69]. While individual studies reported the significance of this molecule in distinguishing SRNS from SSNS, meta-analysis of these two studies was not significant (Fig. 3).

(3) Other serum/plasma markers

Molecules related to steroid metabolism have been studied as biomarkers[60,70]. The level of a downstream signaling molecule of glucocorticosteroids, histone deacetylase (HDAC)2, was lower in SRNS[60], while MIF, the level

Table 2. Serum or plasma markers

Marker	Sample, S or P (Unit)	No. of SSNS (M:F), age	No. of SRNS (M:F), age	Value in SSNS	Value in SRNS	*P* value	AUC	Cutoff	Published year (reference)	Significant
ET1	S (pg/dL)	30	25	18.3±17	52.5±45.8	<0.001	0.88	24.6	Ahmed, 2019	Y
haptoglobin	S (mg/mL)	58	26	30 [26–34]	49 [40-54]	<0.05	0.904	37.935	Yang, 2015	Y
HDAC2 protein†	WB	25 (13:12) 6.7 [3–13]	23 (15:8) 6 [3-13]	0.60±0.11	0.45±0.13	<0.01			Guan, 2018	Y
HDAC2 activity†	S (nmol/L)			32.30±1.42	28.25±1.20	<0.01				Y
IL-8†	S (nmol/L)			102.40±3. 84	125.48±2.78	<0.01				Y
IgA†	S (g/L)	65	22	1.19±0.78	1.10±0.71	n.s.	n/a	n/a	Ling, 2019	N
IgE†	S (g/L)	65	22	216.2 [[59.2, 537.8]]	90.6 [[42.4, 284.0]]	<0.001	n/a	n/a	Ling, 2019	Y
IgG	S (g/L)	24	19	4.7±2.91	2.67±1.65	<0.001	n/a	n/a	Roy, 2009	Y
IgG	S (g/L)	22	19	4.39 [2.96–9.34]	1.03 [0.9–1.67]	<0.001	0.923	2.04	Le Viet, 2019	Y
IgG†	S (g/L)	65	22	3.07±2.9	3.98±2.11	<0.005	n/a	n/a	Ling, 2019	Y
IgM	S (g/L)	24	19	2.6±1.35	3.17±1.54	n.s.	n/a	n/a	Roy, 2009	N
IgM†	S (g/L)	65	22	1.57±0.92	1.59±0.94	n.s.	n/a	n/a	Ling, 2019	N
IgG/IgM ratio	Ratio	24	19	2.7±2.97	1.27±1.25	n.s.	n/a	n/a	Roy, 2009	N
IgG/IgM ratio	Ratio	22	19	2.72 [1.83–6]	0.57 [0.46–1.07]	<0.001	0.892	1.64	Le Viet, 2019	Y
sIL2R	S	23	17	878.9±335.18	1295.7±240.83	<0.001			Youssef, 2011	Y
MDA†	S(nM/mL)	26 (19:7)	7 (3:4) 6.0±0.81	13.4 [8.72–23.0]	17.5 [14.3–29]	0.003			Bakr, 2009	Y
MIF	P(pg/mL)	14	7	414.1	759.7	0.022	0.76	501	Cuzzoni, 2019	Y
NGAL	S(ng/mL)	29	14	80.1 [43.8-163]	103 [50.2-351]	0.34			Ochocinska, 2018	N
NPNT	S (mg/mL)	40	40	4.64±3.05	0.69±0.44	<0.001	0.896	1.215	Watany, 2018	Y
suPAR	S (pg/mL)	108	68	2,153.5±1,167.0	3,744.1±2,226.0	<0.05	0.80	2,578	Peng, 2015	Y
suPAR	S (ng/mL)	25	25	26.22±3.86	66.52±9.7	<0.05	1.00	33.17	Mousa, 2018	Y
TAC†	S (mM/L)	26 (19:7)	7 (3:4) 6.0±0.81	0.85 [0.68–0.91]	0.66 [0.59–0.81]	0.001		0.73	Bakr, 2009	Y
sTNFR1	P (ng/mL)	19	11	3.86±2.16	5.64±3.21	0.21	n/a	n/a	Tain, 2002	N
sTNFR2	P (ng/mL)	19	11	5.67±1.99	7.18±3.13	0.17	n/a	n/a	Tain, 2002	N

†at disease onset.

Abbreviations" n.s., not significant; n/a, not available; ET1, Endothelin-1; HDAC2, histone deacetylase-2; WB, western blot; Ig, immunoglobulin; sIL2R, soluble interleukin-2 receptor; MDA, malondialdehyde; MIF, macrophage migration inhibitory factor; NGAL, neutrophil gelatinase-associated lipocalin; NPNT, nephronectin; suPAR, soluble urokinase Plasminogen Activator Receptor; total antioxidant capacity (TAC), sTNFR, soluble TNF receptors

of a proinflammatory cytokine and counter-regulator of glucocorticoids, was increased[70]. Watany et al. studied nephroneptin, an extracellular matrix protein that is important for kidney development, and found that serum level of nephroneptin was reduced in SRNS[71]. The level of endothelin-1, which is related to the pathogenesis of proteinuria, was higher in SRNS[72]. An Egyptian group studied oxidative stress in NS, reporting that total antioxidant capacity was low and malondialdehyde (MDA), the main indicator of lipid peroxidation, was high in NS, especially in SRNS[73]. However, the serum NGAL concentration was not found to be related to steroid responsiveness in pediatric NS[74].

2) Cellular phenotypes (Table 3)

(1) Lymphocyte population composition

T lymphocyte aberrance has long been considered to be involved in the pathogenesis of idiopathic NS[75]. Recently, the efficacy of rituximab, which depletes CD20+ B cells, raised the speculation that B cells are involved in the pathogenesis of NS[76]. Excluding studies and data involving cell culture, there were three studies comparing the distribution of lymphocyte subsets[62,77,78]; however, one was excluded because they enrolled patients with SSNS in remission[78]. Stachowski et al. reported that when comparing SSNS and SRNS, suppressor-inducer cells (CD45Ra+CD4+) accounted for a higher percentage and memory cells (CD45RO+CD4+) and suppressor-effector cells (CD45RO+CD8+) accounted for a lower percentage in SSNS than in SRNS[77]. Ling et al. found that CD8 lymphocyte populations were larger in SRNS than in SSNS, and the percentage of B cells was higher in SSNS than in SRNS or healthy controls[62]. They also found that at the initial onset of NS, a higher percentage of transitional B cells (CD24highCD38high) could predict the response to steroids, with a cut-off value of 2.05 % of lymphocytes, with an AUC of 0.907 (0.835–0.979).

(2) Other cellular phenotypes

Regarding other cellular phenotype markers, expression of TNF receptors (cTNFR) on granulocytes was investigated to identify differences between SSNS and SRNS, and both cTNFR1 and cTNFR2 expression were decreased in SSNS, while those in SRNS were not different from those in the control condition[59].

3) mRNA expression (Table 4)

Biomarker research using mRNA expression has been consistent with the previously mentioned arenas of biology. JAK/STAT pathways might be involved in the progression

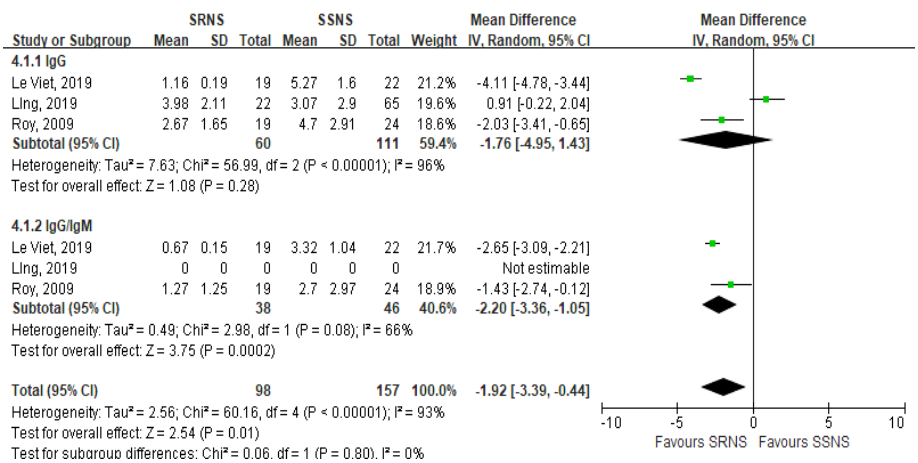

Fig. 2. Prediction of SRNS using immunoglobulin.

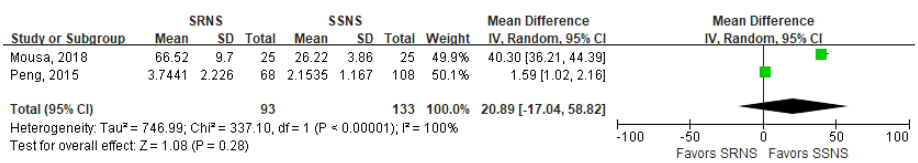

Fig. 3. Prediction of SRNS using suPAR.

of proteinuric glomerular diseases[79]; expression of its main suppressor, suppressor of cytokine signaling (SOCS), was investigated in two studies and found to be increased in SRNS[80,81]. The expression of its receptor glucocorticoid

Table 3. Cellular phenotypes

Marker	Method (unit)	No. of SSNS	No. of SRNS	Value in SSNS	Value in SRNS	*P* value	Author, year	significant
CD45RA+CD4+ suppressor-inducer†				35±9	24±8	<0.05		Y
CD45RO+CD4+ Memory cells†	% in the peripheral blood	25	10	7±4	33±10	<0.001	Stachoswki, 2000	Y
CD45RO+CD8+ suppressor-effector†				26±10	38±12	<0.05		Y
T cell†				70.9±8.9	71.6±7.2	n.s.		N
CD4+T cell†	% of lymphocytes			40.5±8.2	36.9±8.4	n.s.		N
CD8+T cell†				24.3±6.0	29.9±7.6	<0.005		Y
CD4/CD8†	Ratio			1.8±0.6	1.3±0.5	<0.005		Y
Natural killer†		65 (44:21) 5.2±2.9 (onset age)	22 (16:6) 5.5±4.3 (onset age)	5.7±3.0	8.0±4.1	<0.001		Y
B cell†				22.1± 6.7	12.7± 6.1	<0.001	Ling, 2019	Y
Transitional B cells†				5.3±3.8	2.0±1.5	<0.001		Y
Mature B†	% of lymphocytes			22.8±9.6	22.4±8.9	n.s.		N
Memory B†				4.5±2.4	3.5±2.0	n.s.		N
IgM memory B†				1.5±0.8	1.0±0.8	n.s.		N
Switched memory B†				1.3±0.8	1.0±0.4	n.s.		N
cTNFR1†	Expression, %	19	11	43.25±5.77	81.07±5.40	<0.001	Tain, 2002	Y
cTNFR2†	Expression, %	19	11	74.14±7.90	95.21±2.74	0.023	Tain, 2002	Y

†at disease onset.
Abbreviations: SSNS, steroid-sensitive nephrotic syndrome; SRNS, steroid-resistant nephrotic syndrome; n.s. not significant; cTNFR1, cell surface TNF receptors 1; cTNFR2, cell surface TNF receptors 2.

Table 4. mRNA expression

Marker	Method (unit)	No. of SSNS	No. of SRNS	Value in SSNS	Value in SRNS	*P* value	Author, year	Significant
CD80	/β-actin	13	25	1.259 [[0.459, 2.028]]	0.467 [[0.292, 0.654]]	0.021	Mishra, 2017	Y
HDAC2 mRNA	/β-actin	25 (13:12) 6.7 [3–13]	23 (15:8) 6 [3–13]	0.72±0.10	0.60±0.13	<0.01	Guan, 2018	Y
CD3+:GCR	Median %	15	14	70.3±7.71	44.59±8.46	<0.001	Zahran, 2014	Y
CD3+:GCR	Median %	30 (19:11) 5.3 [4–8]	21 (14:7) 6.5 [4–7.6]	56.3 [[51.6–67.9]]	17.6 [[13.5–18.4]]	<0.0001	Hammad, 2013	Y
CD14+:GCR	Median %	30 (19:11) 5.3 [4–8]	21 (14:7) 6.5 [4–7.6]	41.5 [[38.9–46.2]]	17.3 [[11.6–19.4]]	<0.0001	Hammad, 2013	Y
MDR1	Median %	23	17	6.5±2.1	9.2±1.1	<0.001	Youssef, 2011	Y
SOC3 promoter	Methylation status	36 (16:20)	40 (23:17)	Unmethylation 16.7% (n=6)	Unmethylation 82.5% (n=33)	<0.0001	Zaorska, 2016	Y
SOC3	%	34 (18:16) 10.5 [4-16]	20 (11:9) 11.3 [4-17]	n:a (Data not given)	Increased by 22.5	0.0005	Ostalska-Nowicka, 2011	Y
SOC5	%	34 (18:16) 10.5 [4-16]	20 (11:9) 11.3 [4-17]	n:a (Data not given)	Increased by 13.6	0.0005	Ostalska-Nowicka, 2011	Y
TLR-3	/β-actin	13	25	1.128 [[0.337, 1.685]]	0.324 [[0.274, 0.652]]	0.015	Mishra, 2017	Y
TLR-4	/β-actin	13	25	0.805 [[0.300, 1.537]]	0.226 [[0.193, 0.563]]	0.015	Mishra, 2017	Y

Abbreviations: HDAC2, Histone deacetylase-2; TLR, Toll-like receptor; CD80, cluster of differentiation 80; SSNS, steroid-sensitive nephrotic syndrome; SRNS' steroid-resistant nephrotic syndrome, IQR, interquartile range; SOC3, suppressor of cytokine signaling 3 gene; GCR, glucocorticoid receptor; MDR1, multidrug resistant gene-1; sIL2R, serum soluble interleukin-2 receptor.

receptors (GCR), multidrug resistant gene *MDR1*, and HDAC2 expression were studied[60,61,82,83], all of which were statisticaly significant. CD80 and toll-like receptors (TLRs) were identified to be associated with the pathogenesis of NS[84], and their expression in peripheral blood mononuclear cells was decreased in SRNS58. In short, *MDR1* and SOC 3,5-related genes were increased in SRNS and all the others were more increased in SSNS then in SRNS.

3. Genotype markers

1) Progression of kidney disease-related genes

In the early 21st century, associations of *ACE* polymorphism, the I or D allele, and kidney-related health problems were actively investigated[85,86]. There are three possible genotypes, II, ID, and DD; genotype DD or D allele is known to be associated with increased ACE activity[85-87]. Regarding steroid response in pediatric NS, 10 studies were found[88-96]. These studies were analyzed to explore the possible associa-

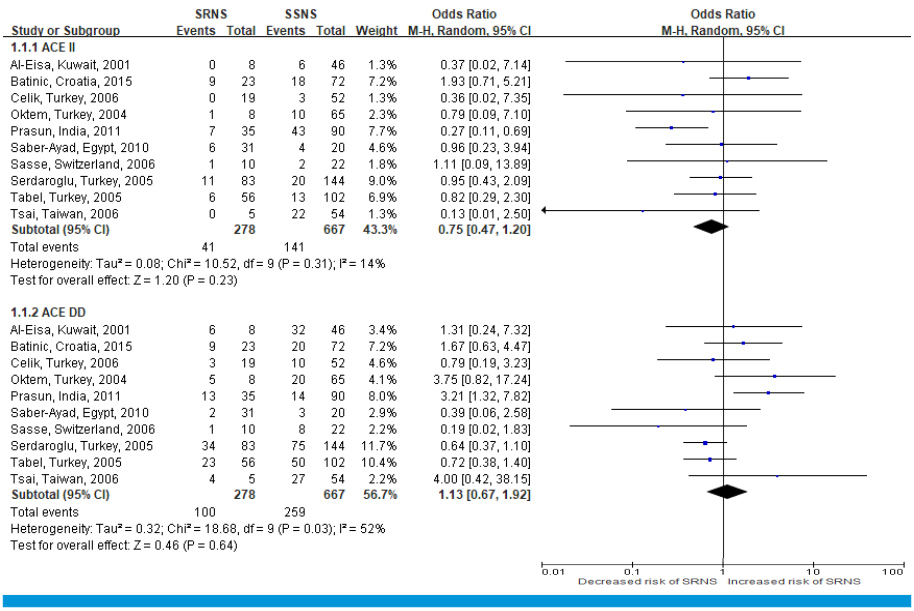

Fig. 4. Distribution of ACE polymorphism and the risk of SRNS.

Table 5. Other genetic polymorphisms

Marker	Polymorphism	No. of SSNS (M:F)	No. of SRNS (M:F)	Value in SSNS	Value in SRNS	OR <95% CI>	*P* value	Author, year	Country	Significant
AT1R	A1166C	102	56				n.s.	Tabel, 2005	Turkey	N
AGT	T704C (Met235Thr)	102	56		More TT	4,837 <1,723–13,577>	0.01	Tabel, 2005	Turkey	Y
APOE	ε	87	20		ε2 allele, ε2/3	<0.05		Atttila, 2002	Turkey	Y
ENDRA	rs5333 (T/C)	61	39		More C allele	1.94 <1.02–3.69>	0.04	Ezzat, 2019	Egypt	Y
GLCCI1	rs37972 and rs37973	117	94				n.s.	Cheong, 2012	Korea and USA	N
IL4	C590T	115	35	More CC	More TT	6.46	0.02	Jafar, 2011	India	Y
NR3C1		83	35				n.s.	Ye, 2006	China	N
SXR (NR1I2)	rs3842689 (In/Del)	47 (28:19)	9 (6:3)		Del/Del	20.57 <2.10–200.81>	0.009	Turolo, 2016	Italy	Y
TRPC6	rs3824934 (-254C>G)	23 (19:4)	28 (19:9)		More G	2.29 <1.01–5.18>	0.046	Kuang, 2013	China	Y
Uteroglobin	G38A	84 (46:38)	52 (22:30)	More GG	More AA	n.s.		Demircioglu, 2018	Turkey	N
VDR	c.1025-49G>T, c.1056T>C	62 (39:23)	16 (13:3)			n.s.		Al-Eisa, 2016	Kuwait	N

tion between the DD or II genotype and the phenotypes of SRNS and SSNS (Fig. 4). Statistically, the distribution of both genotypes did not differ between SRNS and SSNS. Other genes involved in the renin-angiotensin-aldosterone system (RAS) were also evaluated[96]; T alleles of the T704C polymorphism of *AGT* were more common in SRNS in one study (Table 5)[95].

Endothelin-1 has been speculated to be involved in the pathogenesis of proteinuria and glomerulosclerosis[97]. Polymorphism of the endothelin receptor type A gene (*ENDRA*) was significantly associated with SRNS in one study[98]. Apolipoprotein E (*ApoE*) polymorphism was also found to be significant[99].

2) Steroid receptor- or metabolism-related genes

Resistance to steroid treatment might stem from steroid receptor aberrations or impaired metabolism of the medication. Glucocorticoid receptors, *NR3C1*[100] or *GLCCI1*[101], and genes related to the metabolism of this medication, *MDR1*[102-106], *MIF*[102,107,108], and *CYP3A5*[104,105], were investigated for the association of their polymorphisms and the response to steroids in pediatric NS.

(1) *MDR1* (*ABCB1*)

MDR1 encodes P-glycoprotein, which eliminates steroids from the cells. In a Korean study and an Egyptian study, the C allele of the C1236T polymorphism was associated with a better response to steroid treatment[96]. Studies in India and Tunisia reported that the proportion of homozygous mutants of G2677T/A, a polymorphism causing an amino acid substitution (Ala899Ser/Thr) in P-glycoprotein, was higher in SRNS than in SSNS[103,105]. Another Egyptian study found that the frequency of minor alleles of G2677T/A was higher in SRNS than in SSNS[106], while a Turkish study did not find any association between the most frequent polymorphisms of C1236T, G2677T/A, or C3435T of *MDR1* and steroid responsiveness[104]. Meta-analysis of data from these five studies revealed that the major alleles of C1236T and G2677T/A seem to be protective against SRNS (Fig. 5) However, this difference was not statistically significant. However, having two copies of the minor allele of G2677T/A was associated with increased risk of SRNS [OR 1.6 (1.01–2.50)]. The frequency of the C3435T polymorphism did not differ between SSNS and SRNS. Haplotype analysis of the *MDR1* gene and its above-mentioned three polymorphisms (C1236T, G2677T/A, and C3435T) was performed in four of the studies[102,103,105,106]; two studies found that the frequency of the TGC haplotype was significantly lower in SSNS[102,106]. Another study reported that the haplotype of TAT increased the risk of SRNS [OR 2.69 (1.12–8.79); P= 0.044][105].

(2) Macrophage migration inhibitory factor (*MIF*) and *CYP3A5*

MIF is a proinflammatory cytokine but is also the "physiological counter-regulator of the immunosuppressive effects of glucocorticoids"[108]. The promoter polymorphism of G-173C, known to be associated with the amount of MIF production and susceptibility to inflammatory diseases, was investigated in four studies[102,107,109,110]. According to a meta-analysis, the *MIF*-173 CC genotype seemed more common in SRNS than in SSNS and -173 GG genotype appeared protective; however, the results were not statistically significant (Fig. 6). Świerczewska et al. studied other MIF polymorphisms, but no significance was found[110]. *CYP3A5* encodes for the cytochrome P450 enzyme involved in the metabolism of many exogenous and endogenous compounds. Three studies were found to analyze the effect of polymorphism of this enzyme[104,105,111], and no significant results were found.

Polymorphisms of the glucocorticoid receptor gene (*NR3C1*) and glucocorticoid-induced transcript 1 gene (*GLCCI1*) were not significant[100,101], while those of the steroid and xenobiotic receptor (*SXR, NR1I2*) were significant (Table 5)[112].

4.Pathogenesis of NS-related genes

1) Cytokines

Cytokines have long been speculated to be involved in the pathogenesis of NS[75]. Polymorphisms of *TNFa* and IL-6 have been evaluated in a few studies[113-115]; minor alleles were more common in SRNS, although the differences were not all statistically significant (Fig. 7). Another Th2 cytokine, IL-4, was also found to be significant[113].

2) Podocin and *TRPC6*

Podocin, encoded by NPHS2, is a membrane protein of glomerular epithelial cells, podocytes, linking nephrin of the slit diaphragm and intracellular signaling of podocytes.

Mutations in *NPHS2* are the most common cause of FSGS, at least in Caucasian populations[116,117]. The polymorphism R229Q is a well-known functional polymorphism that was reported to be associated with late-onset FSGS[118,119] or predisposition to develop FSGS[120,121]. Five studies were found to compare the allele frequency of this polymorphism between SSNS and SRNS[117,118,122-124], and the difference did not reach significance in the meta-analysis using a random effects model (Fig. 8). Polymorphism -254C>G of *TRPC6*, another causative gene of familial FSGS[125], was assessed in

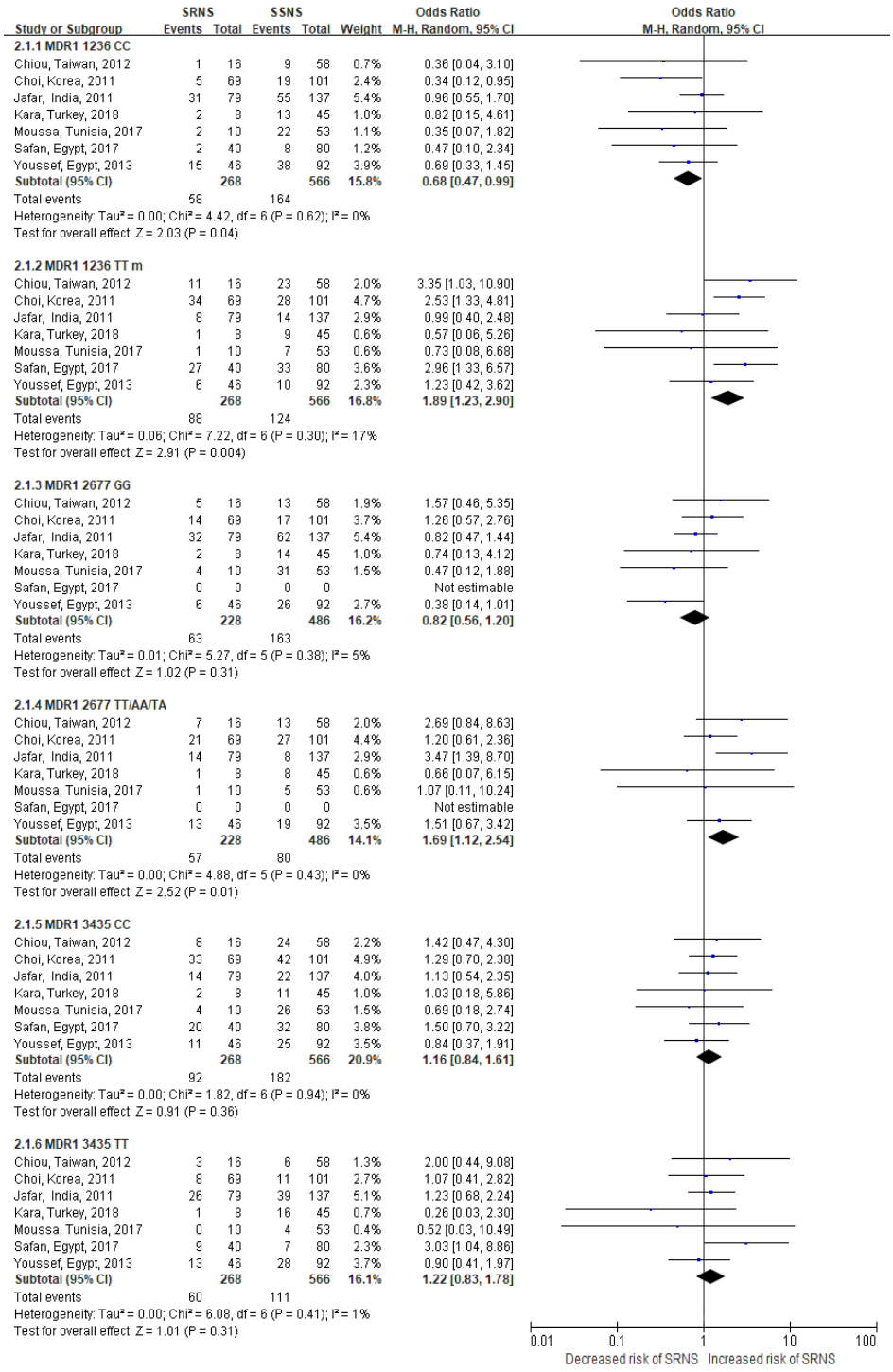

Fig. 5. Distribution of *MDR1* polymorphism and the risk of SRNS.

one study that reported marginally meaningful significance[126] (Table 5).

5. HLA allele frequencies

Regarding HLA allele frequencies in lieu of steroid responsiveness in pediatric NS, the full text was available for two Indian studies[127,128]. One study typed HLA class II alleles at DR and DQ loci and found that the DR-β1*150X-DQ-β1*060X haplotype was significantly more frequent in SRNS than in SSNS[127] (Table 6).

Discussion

Regarding biomarkers predicting SSNS and SRNS, urinary markers were the first to be investigated[129]. The proteinuria selectivity index (SI, the ratio of immunoglobulin G clearance to transferrin or albumin clearance) was originally devised to predict glomerular damage; SI ≤0.01 was supposed to predict pathological findings of minimal change disease in patients with heavy proteinuria[130]. It was the first candidate urinary marker evaluated according to the literature search[41,129-131], but the full texts was not available or its statistical significance was not reported. According to the present systematic review, urinary markers with consistent results were ANX5[25,28,48], NGAL[49-51], and VDBP

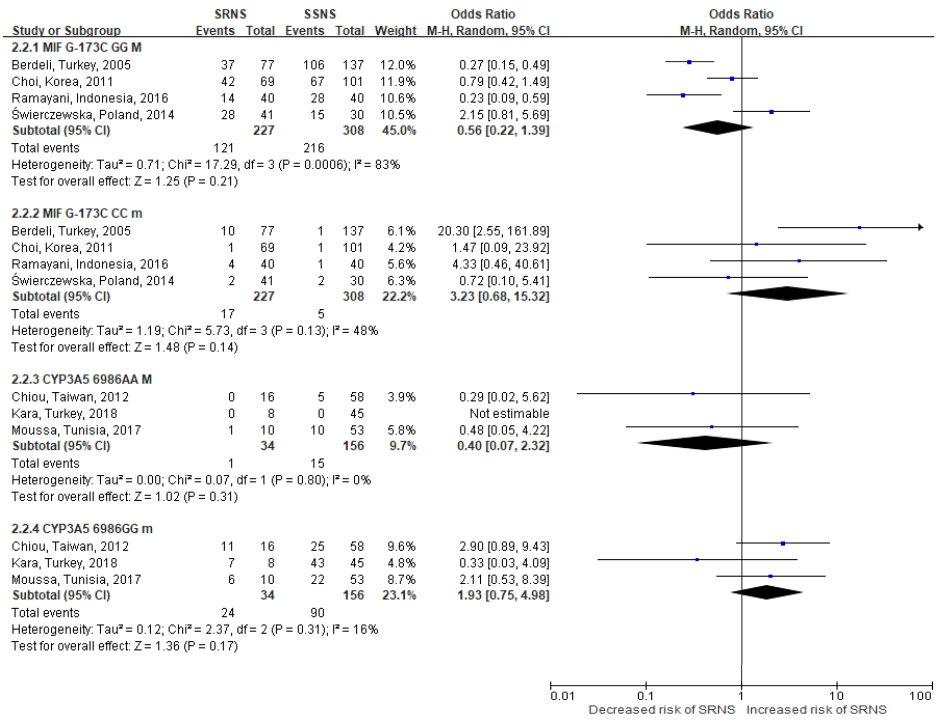

Fig. 6. Distribution of *MIF* and *CYP3A5* polymorphism and the risk of SRNS.

Table 6. HLA allele frequencies

Marker	Method (unit)	No. of SSNS	No. of SRNS	Value in SSNS	Value in SRNS	*P* value	Author, year	Significant
HLA DR-β1*150X-DQ-β1*060X	Allele frequency %	83	17	14.15	38.24	0.001	Gulati, 2007	Y
HLA-DRB1*07	Allele frequency% (n)	76 (45:31) 4.4±0.3	107 (62:45) 4.14±0.2	35.52 (54)	27.57 (59)	0.029	Ramanathan, 2016	Y
HLA-DRB1*10				09.86 (15)	4.20 (09)	0.025		Y
HLA-DQB1*02				30.92 (47)	23.83 (51)	0.058		N
HLA-DQB1*05				21.05 (32)	29.90 (64)	0.018		Y
HLA-DQB1*06				17.10 (26)	24.76 (53)	0.039		Y
HLA-DQB1*0301, 0304 (DQ7)				24.34 (37)	14.48 (31)	0.007		Y

[51,54,132] and these were markers of renal tissue damage. However, it can be speculated that these markers may have simply reflected kidney damage or the underlying pathology instead of predicting steroid responsiveness, because sclerosis is more progressed in SRNS than in SSNS. Urinary levels of NGAL and VDBP negatively correlated with eGFR, which would decrease with kidney damage[49,50,54]. However, investigators have asserted otherwise, by showing that VDBP and NGAL were significantly elevated in SRNS patients with normal eGFR (>100 mL/minute/1.73 m^2)[49,50,54]. No study has assessed the correlation between urine ANX5 levels and eGFR. One important concern regarding urinary markers is that these markers may only indicate the severity of proteinuria[25,28]. Supporting this concern, urinary VDBP and ANX5 showed positive correlations with microalbuminuria and proteinuria[25,28,54]. However, urine VDBP distinguished SRNS independent of proteinuria[51]. Regarding ANX5, there were only conference ab-

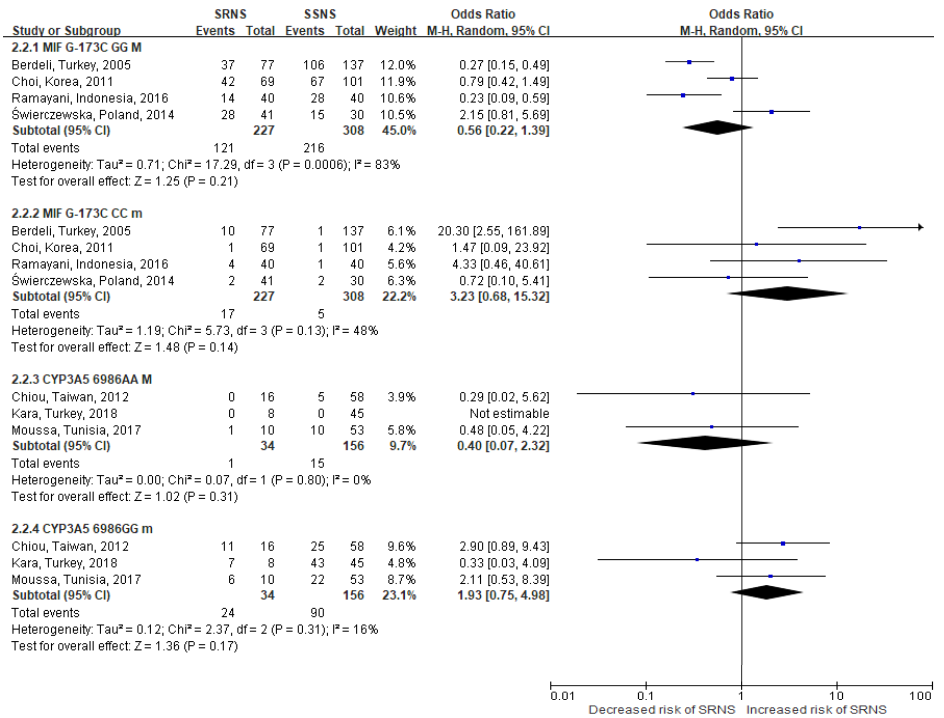

Fig. 7. Distribution of TNFα and IL-6 polymorphism and the risk of SRNS.

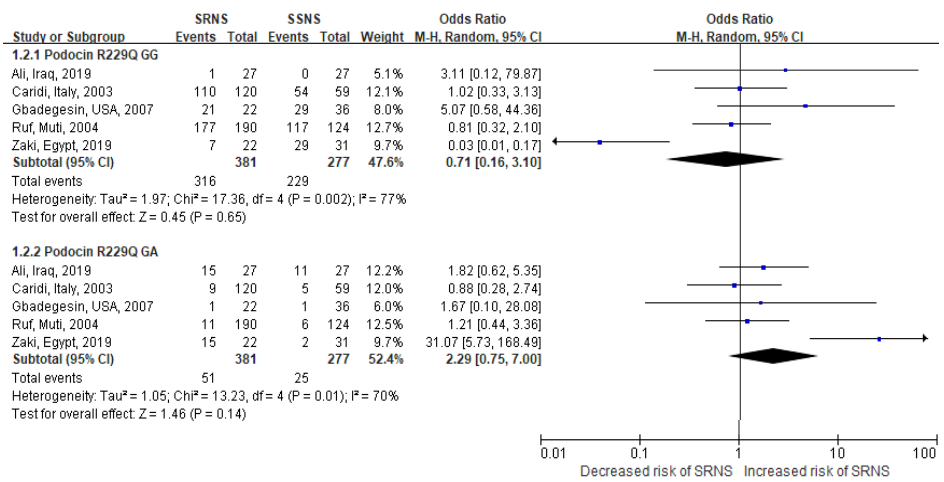

Fig. 8. Distribution of podocin polymorphism and the risk of SRNS.

stracts[25,28], and NGAL was found not to be correlated with proteinuria[49]. PBSA[56], AAT[40], APO A1[46], and prealbumin [51] did not have contradicting reports, but this may have been due to a lack of follow-up studies. Interestingly, APO A1, a major component of HDL, is increased in SSNS, and the investigators suggested that this molecule might not be detected because of oxidation and fragmentation in SRNS [46]. A recent study by Bennett et al. proposed using panel models to calculate the risk score of the SRNS[51]. Could these markers be used for treatment-naïve patients? Only AAT[40], ANX5[28], NAG[44], PBSA[56], and RBP[47] were studied in treatment-naïve patients and have not been validated.

While urinary markers have been sought for since 1980, serum biomarkers have begun to be investigated in this century. Idiopathic NS has been considered a disease of the immune system, especially T cells; therefore, cytokines and lymphocyte subsets were initially studied. While there are many studies demonstrating the association between NS and the predominance of Th2[133-135], only few studies have investigated lymphocyte subsets, cytokines, or their receptors as biomarkers for predicting steroid responsiveness[59, 61,62,77,78,113]. Some of the markers confirmed the pro-inflammatory status of SSNS, while those of SRNS were similar to those of the controls[59,136,62]. Other mechanisms of kidney disease progression have also been investigated as well[58,71-73]. Among the significant markers, the significance of serum IgG/IgM may simply reflect the severity of NS[63,64]. Regarding suPAR, meta-analysis revealed a lack of significance, although individual studies have reported the significance of its prediction capacity.

Recently, the Midwest Pediatric Nephrology Consortium reported two studies using proteomics and metabolomics to investigate biomarkers of steroid responsiveness in pediatric NS[137,138]. They found that VDBP and apolipoprotein L1 (APOL1) in pre-treatment samples could differentiate SSNS and SRNS; hemopexin, adiponectin (ADIPOQ), and sex hormone-binding globulin (SHBG), in addition to VDBP and APOL1, could distinguish SRNS from SSNS when post-treatment samples were investigated. The researchers proposed a panel of VDBP, ADIPOQ, and matrix metalloproteinase 2 (MMP-2) to predict steroid responsiveness, and the panel could distinguish SRNS and SSNS with an AUC of 0.78 (P=0.003)[137]. In a metabolomics study, the same group identified creatinine, glutamine, and malonate as candidate biomarkers and used these markers along with age to draw ROC curves with an AUC >0.8[137]. However, these studies did not provide measured values in patients and were therefore excluded from this systematic review.

The influence of polymorphisms in genes related to the progression of kidney diseases (genes related to RAS, endothelin receptor, and ApoE), glucocorticoid metabolism (*MDR1, MIF, CYP3A5, NR3C1, GLCCI1, SXR*), and the pathogenesis of nephrotic syndrome (cytokines, podocin, or *TRPC6*) on the response to steroids in pediatric NS were studied. I/D polymorphisms of *ACE* were not significant, as previously reported[41], while polymorphisms of *AGT, ENDRA*, and ApoE were significant. However, these were the results of single studies; therefore, verification is necessary before drawing any conclusions. In contrast, minor alleles of *MDR1* polymorphisms C1236T (rs1128503) and G2677T/A (rs2032582) were more common in SRNS according to a meta-analysis of several studies, as previously reported in a meta-analysis[139], where multiple comparisons negated the significance of polymorphisms of G2677T/A using slightly different source studies than this study. Interestingly, polymorphism of the steroid and xenobiotic receptor (*SXR*) was significant, but there was no follow-up study. These results deserve notice; in a population with a higher proportion of minor alleles, pre-screening before starting steroid therapy might help predict steroid response. Among genes related to the pathogenesis of NS, polymorphism of IL-6 was significant, although the number of studies was too small to be of importance. Serum IL-6 levels were higher in patients with NS other than minimal change[140], and the IL-6-related pathway was found to be related to SRNS in an anecdotal study using transcriptome profiling[141]. Podocytes express IL-6[142]. However, other studies have reported that the expression of IL-6 by monocytes in NS patients was not different from that in controls [136] or even lower than that in controls[143]. Further studies are necessary to ascertain the significance of this finding. The findings of studies regarding genotypes are quite heterogeneous, probably because of different genotype distributions among the target populations, in other words, ethnic differences or selection bias. For example, Zhou et al. reported that the DD genotype of ACE was associated with SRNS in Africans based on one study[144], but not in

Asians or Caucasians. The II genotype was found to be associated with a decreased risk of SRNS in Asians and Caucasians by Zhou et al., but re-analysis comparing SRNS and SSNS including more recent studies revealed otherwise. Podocin polymorphism is another example; the frequency of R229Q of podocin is 0.01–7%[120]; therefore, its effect on the target population would be heterogeneous as well, which might explain the insignificance of this minor allele in the meta-analysis. Since the clinical implications of each polymorphism would differ by population, understanding the genetic characteristics of the target population may be helpful in applying the above findings.

In summary, along with the molecules implying kidney damage, biomarkers related to steroid metabolism-associated biomarkers may have a potential as a prediction biomarker for steroid responsiveness in children with NS. VDBP was found both as a serum marker in an omics study [138] and a urinary marker as well[51,54] although further validation is required. More attention and efforts to investigate the clinical significance is necessary.

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Conflicts of interest

No potential conflict of interest relevant to this article was reported.

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