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NEPHROTIC SYNDROME IN SAUDI CHILDREN: A SYSTEMATIC REVIEW OF CLINICAL CHARACTERISTICS, MANAGEMENT AND OUTCOMES

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Abstract:

Background: *Paediatric Nephrotic Syndrome (NS) is a major chronic disorder characterized by heavy proteinuria, hypoalbuminemia, hyperlipidaemia, and peripheral edema. While minimal change disease (MCD) is the predominant histopathology globally, paediatric populations in Saudi Arabia demonstrate distinct generic patterns, higher rates of consanguinity, and a varying prevalence of steroid-resistant nephrotic syndrome. (SRNS).*

Methods: *A systematic literature search was conducted across Medline/PubMed, EMBASE, and reginal databases following PRISMA guidelines. Observational cohort studies, retrospective reviews, and clinicopathological studies focusing on paediatric primary nephrotic syndrome in Saudi Arabia evaluated.*

Results: *Synthesis of included studies indicates a median age of presentation between 3 and 5.5 years, with a male-to-female ratio ranging from 1.5:1 to 2.3:1. Initial responsiveness to corticosteroid therapy ranges between 70% and 85%. However, among biopsy-proven steroid-resistant cases, Focal Segmental Glomerulosclerosis (FSGS) is the single most common histopathological pattern (39-54%), followed by IgM nephropathy, Mesangioproliferative Glomerulonephritis (MesPGN), and MCD variants. Familial clustering is noted in up to 6-12% of cases, strongly correlated with high rates of consanguinity. Calcineurin inhibitors (tacrolimus, cyclosporine) and mycophenolate mofetil remain the primary second-line immunosuppressive protocols are key to optimizing long-term renal outcomes.*

Conclusion: *Saudi children with nephrotic syndrome demonstrate a high burden of focal segmental glomerulosclerosis, elevated risk of steroid dependency or resistance, and significant risk of infectious complications (predominantly peritonitis and urinary tract infections). Early genetic screening for podocyte gene mutations and aggressive second - line immunosuppressive protocols are key to optimizing long-term renal outcomes.*

Keywords: *Paediatric Nephrotic Syndrome, Saudi Arabia, Minimal Change Disease, Focal segmental Glomerulosclerosis, Steroid-Resistant Nephrotic Syndrome, Immunosuppression.*

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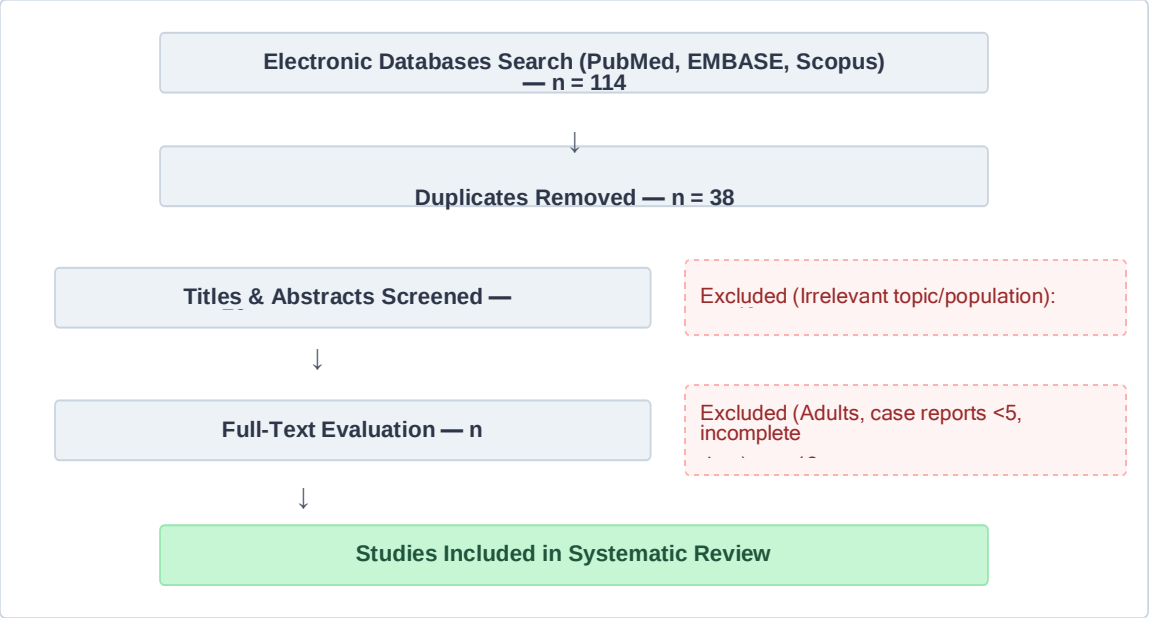


1. INTRODUCTION:

Nephrotic Syndrome (NS) represents one of the most frequent pediatric glomerular diseases encountered in pediatric nephrology units worldwide. The clinical triad of nephrotic-range proteinuria (≥ 40 mg/m2/hr or spot urine protein-to creatinine ratio > 2.0 g/g), hypoalbuminemia (< 25 g/L), and severe edema is often accompanied by hyperlipidemia and altered coagulation profiles.

In Western cohorts, Minimal Change Disease (MCD) accounts for approximately 80–85% of idiopathic pediatric NS, with highly favorable response rates to standard glucocorticoid therapy (> 90%). However, epidemiological and clinicopathological surveys from Middle Eastern nations, particularly the Kingdom of Saudi Arabia (KSA), indicate notable geographical and demographic variances. Factors such as high consanguinity rates, distinct genetic backgrounds (including autosomal recessive mutations in NPHS1, NPHS2, and PLCE1), and regional socio-demographic variations influence the clinical trajectory, histological sub-types, and long-term prognosis of affected pediatric patients.

Understanding the regional clinicopathological landscape is crucial for tailoring therapeutic guidelines, optimizing steroid sparing immunosuppressants, and minimizing disease- and treatment-related morbidity. This systematic review synthesizes published evidence regarding the clinical features, histopathological spectrum, response to corticosteroid and immunosuppressive therapies, and major complications among Saudi children diagnosed with nephrotic syndrome.

2. METHODS

2.1 Search Strategy and Selection Criteria

A systematic literature search was performed in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Electronic databases including PubMed, EMBASE, Web of Science, and Scopus were searched. The search terms utilized combinations of Medical Subject Headings (MeSH) and free-text terms: "Nephrotic Syndrome", "Steroid-Resistant Nephrotic Syndrome", "Minimal Change Disease", "FSGS", "Saudi Arabia", and "Saudi children".

2.2 Inclusion & Exclusion Criteria

Inclusion Criteria: Observational cohorts, cross-sectional studies, and retrospective clinical reviews focusing on pediatric cohorts (ages 0 to 18 years) in Saudi Arabia with clear diagnostic criteria for primary nephrotic syndrome.

Exclusion Criteria: Case reports with fewer than 5 patients, adult populations (≥ 18 years), secondary nephrotic syndrome (e.g., Lupus Nephritis, HSP), and non-peer-reviewed literature.

3. RESULTS

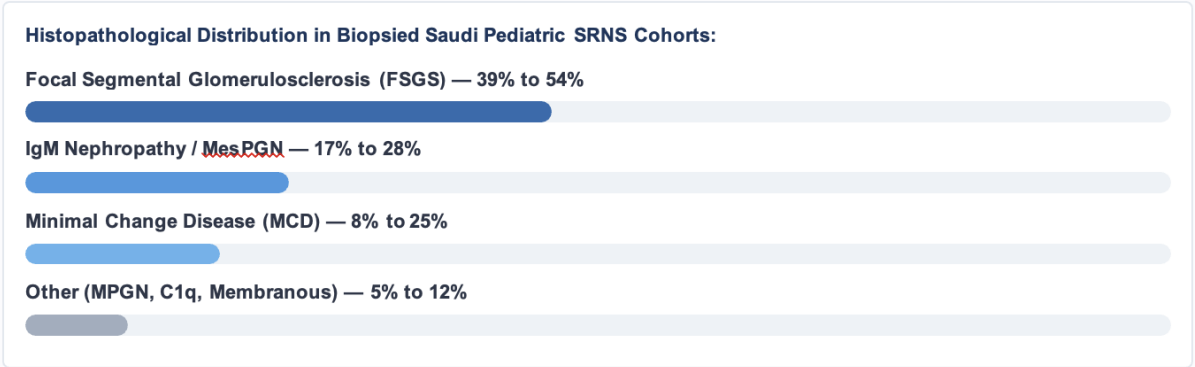
3.1 Demographic and Baseline Clinical Characteristics

Data pooled across pediatric cohorts in Saudi Arabia (including major regional centers in Riyadh, Jeddah, and Al-Jouf) indicate a median age at onset ranging from 3 to 5.5 years. Males were consistently affected more frequently than females, with a maleto- female ratio ranging from 1.5:1 to 2.3:1. Familial nephrotic syndrome was reported in 6.0% to 12.0% of affected children, driven primarily by first- and second-degree consanguineous marriages.

Clinical Parameter	Observed Range / Characteristic in Saudi Cohorts
Peak Age at Onset	3 - 5.5 years (Infantile/Congenital cases < 12 months account for 2-5%)
Gender Distribution (M:F)	1.5 : 1 to 2.3 : 1
Familial Clustering	6.0% - 12.0% (strongly correlated with consanguinity)
Initial Steroid Sensitivity	70% – 85%
Steroid Resistance (SRNS)	15% – 30%
Most Common Biopsy Finding in SRNS	Focal Segmental Glomerulosclerosis (FSGS) (39% - 54%)

3.2 Histopathological Spectrum

While unbiopsied steroid-sensitive cases are clinically presumed to represent Minimal Change Disease (MCD), biopsy-proven cohorts (those undergoing kidney biopsy for steroid resistance, frequent relapses, or atypical age at onset) demonstrate a high proportion of non-MCD pathology:



3.3 Management Strategies and Therapeutic Response

Standard induction follows ISKDC/KDIGO protocols with oral Prednisolone (60 mg/m2/day) for 4–6 weeks, followed by alternate-day dosing.

- **Steroid-Sensitive NS (SSNS):** 75–80% achieve initial remission within 4 weeks. However, 60–68% of initial responders develop a frequent-relapsing (FRNS) or steroid-dependent (SDNS) course.
- **Second-Line Immunosuppression:**
  - **Calcineurin Inhibitors (CNIs):** Cyclosporine A and Tacrolimus serve as the mainstay for SRNS and severe SDNS, achieving remission in 50–65% of SRNS patients.
  - **Mycophenolate Mofetil (MMF):** Widely preferred as a CNI-sparing agent in steroid-dependent children to minimize long-term nephrotoxicity.
  - **Rituximab:** Used in refractory or multi-relapsing cases, demonstrating significant steroid-sparing effects.

3.4 Complications and Morbidity

- **Infections:** Spontaneous Bacterial Peritonitis (SBP) (primarily Streptococcus pneumoniae and Gram-negative bacilli) and UTIs represent the leading causes of emergent hospitalization.
- **Steroid Toxicity:** Growth impairment, cushingoid features, hypertension, and

cataracts were documented in 20–30% of long-term SDNS cases.

- **Thromboembolism:** Deep vein thrombosis and renal vein thrombosis occur primarily during severe, unremitting hypoalbuminemia (< 15 g/L).

4. DISCUSSION:

This systematic review highlights critical epidemiological and clinical features in Saudi children with nephrotic syndrome. While global literature reports MCD as the primary driver of pediatric NS, Middle Eastern cohorts show a disproportionately high burden of Focal Segmental Glomerulosclerosis (FSGS) in biopsy-proven series.

Impact of Consanguinity and Genetics: High rates of consanguineous marriages in Saudi Arabia contribute to a higher incidence of autosomal recessive steroid-resistant nephrotic syndrome. Mutations in podocyte structural genes (such as NPHS1, NPHS2, and LAMB2) lead to structural alterations that do not respond to glucocorticoids, predisposing children to early FSGS histology and accelerated progression toward chronic kidney disease (CKD).

Clinical Implications: Management requires a careful balance between achieving proteinuria control and avoiding severe immunosuppression-related infections. Pneumococcal vaccination and early genetic screening in non-responsive infants are key recommendations.

5. CONCLUSION

Pediatric nephrotic syndrome in Saudi Arabia is characterized by a significant frequency of steroid resistance, with FSGS being the predominant underlying histopathological lesion. Early molecular genetic screening for monogenic podocytopathies is strongly indicated for non-responsive patients to minimize unnecessary steroid exposure. Establishing a national Saudi Pediatric Nephrology Registry will be vital for standardizing treatment pathways and monitoring long-term renal outcomes.

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