VER
Vascular & Endovascular Review

Aortic Root Dilatation In children with Idiopathic Nephrotic Syndrome

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ABSTRACT

Childhood idiopathic nephrotic syndrome (INS) is a common glomerular disorder marked by proteinuria, hypoalbuminemia, edema, and hyperlipidemia. While most cases are steroid-sensitive, frequent relapses and cumulative corticosteroid exposure predispose patients to long-term complications. Cardiovascular disease (CVD) is a major concern, driven by dyslipidemia, thrombogenesis, inflammation, and persistent proteinuria. Aortic root dilatation, defined as a z-score >2 at the root, sinotubular junction, or ascending aorta, is an emerging cardiovascular manifestation with serious implications, including dissection, aneurysm, and rupture. This review explores the epidemiology, pathophysiology, and genetic background of nephrotic syndrome, the mechanisms linking it to cardiovascular remodeling, and the specific risk of aortic root dilatation in affected children. Evidence highlights a prevalence of aortic dilatation of up to 31% in children on dialysis or post-transplant, compared with 6% in early CKD and only 2.3% in the general pediatric population. Contributing factors include hypertension, chronic inflammation, mineral metabolism disorders, endothelial dysfunction, and malnutrition. Early recognition, vigilant monitoring, and integrated management strategies are essential to reduce morbidity and mortality. This review aims to summarize current evidence on the relationship between idiopathic nephrotic syndrome in children and aortic root dilatation. It explores the underlying mechanisms, prevalence, risk factors, diagnostic approaches, and clinical implications, with the goal of highlighting the importance of early recognition, monitoring, and integrated management to prevent severe cardiovascular outcomes.

KEYWORDS: Idiopathic nephrotic syndrome, Aortic root dilatation, CKD, Pediatric nephrology.

How to Cite: Khaled Abdallah Abdel Basser, Doaa Mohamed Salah, Ebtessam Ahmed Abdel Basset, Maha Elsareea Mohamed, (2025) Aortic Root Dilatation In children with Idiopathic Nephrotic Syndrome, Vascular and Endovascular Review, Vol.8, No.3s, 183-189.

INTRODUCTION

Childhood nephrotic syndrome is among the most frequent pediatric kidney diseases, defined by proteinuria, edema, hypoalbuminemia, and hyperlipidemia. Most patients are steroid-sensitive but often experience frequent relapses or prolonged prednisone therapy **(Abdelhamid et al., 2024).** Although long-term renal function and remission are usually preserved, cumulative steroid exposure and recurrent proteinuria-hyperlipidemia increase the risk of accelerated cardiovascular disease **(Boyer et al., 2022)**.

Cardiac involvement may also result from malnutrition and inflammation due to persistent proteinuria. Aortic dilatation, defined as a z-score >2 (97.7th percentile) at the root, sinotubular junction, or ascending aorta by echocardiography, is clinically significant as it may precede dissection, aneurysm, or rupture, conditions associated with high morbidity and mortality, particularly in hypertensive patients **(Namgoong 2020).**

Idiopathic Nephrotic Syndrome in Children

Nephrotic syndrome (NS) is common in children, presenting with severe proteinuria, hypoalbuminemia, and generalized edema. Despite similar presentation, outcomes vary due to unpredictable drug response and risk of renal failure, reflecting distinct pathologies **(Elmaghraby et al., 2020)**. Histology ranges from minimal change disease (MCD) to focal segmental glomerulosclerosis (FSGS), both showing podocyte slit diaphragm effacement as the cause of proteinuria. Whether FSGS evolves from MCD or represents a separate entity remains debated **(Vincenti et al., 2023).**

Idiopathic vs Secondary NS

Childhood NS is idiopathic (iNS) when no cause is identified, while secondary NS arises from genetic, infectious, or drug-related factors. Genetic variants affecting podocyte or glomerular proteins are found in 66% of congenital and infantile NS, 30% of children, and 10–15% of young adults **(Hashim et al., 2025)**. Viral and drug-related secondary NS are also recognized. Differentiating iNS from secondary NS is essential, as genetic NS rarely responds to drugs **(Morello et al., 2020).**

Clinical Definitions

NS is diagnosed with edema plus proteinuria >40 mg/m²/h, protein–creatinine ratio ≥2000 mg/g (≥200 mg/mmol), or ≥3+ dipstick protein, with serum albumin <2.5 g/dL (25 g/L) **(Lebel et al., 2020).**

- **Remission**: negative/trace dipstick, proteinuria <4 mg/m²/h, or protein–creatinine ratio <200 mg/g (20 mg/mmol) for 3 days **(Croitoru and Balgradean 2022).**
- **Relapse**: proteinuria >40 mg/m²/h, protein–creatinine ratio >200 mg/g, or 3+ albumin for 3 days.
- **Frequent relapses**: ≥2 in 6 months or ≥4 in 12 months.
- **Steroid-dependent NS**: relapse during tapering or within 2 weeks of stopping steroids.
- **Steroid-resistant NS**: persistent proteinuria after 8 weeks of 60 mg/m² or 2 mg/kg steroids, excluding infection/non-adherence **(Gulati and Gulati 2019).**

CAUSES OF SECONDARY NS

Glomerular Disorders

IgA nephropathy, Henoch–Schönlein purpura, membranoproliferative GN, lupus nephritis, and post-infectious GN are common. Other causes include immune complex GN, C1q nephropathy, thin basement membrane disease, membranous nephropathy, sickle-cell nephropathy, thrombotic microangiopathy, and interstitial nephritis **(Wang and Chen 2024).**

Infections

Hepatitis B, C, HIV-1, malaria, syphilis, toxoplasmosis, and varicella are established causes **(Nandlal et al., 2019).**

Drugs

NSAIDs, bisphosphonates, D-penicillamine, mercury, gold, lithium, rifampicin, and sulfasalazine can induce NS **(Aly et al., 2022).**

T-Cell Malignancies

Hodgkin's lymphoma, thymoma, and leukemias may trigger NS via immune mechanisms **(Noone et al., 2018).**

Incidence

NS incidence ranges 1.15–16.9/100,000 children, highest in South Asians. Steroid resistance varies 2.1–27.3% depending on geography and management. In Egypt, incidence and steroid resistance are rising, with more complications, hospitalizations, immunosuppressive use, and renal deterioration **(Ademola et al., 2022).**

PATHOPHYSIOLOGY

Podocyte and Filtration Barrier

The filtration barrier consists of podocytes, basement membrane, and fenestrated endothelium. Podocyte actin cytoskeleton maintains integrity; injury causes albuminuria. Podocyte effacement and gene mutations in slit diaphragm, actin, mitochondria, and basement membrane proteins cause proteinuria (Figure 1) **(Pitekova et al., 2023).**

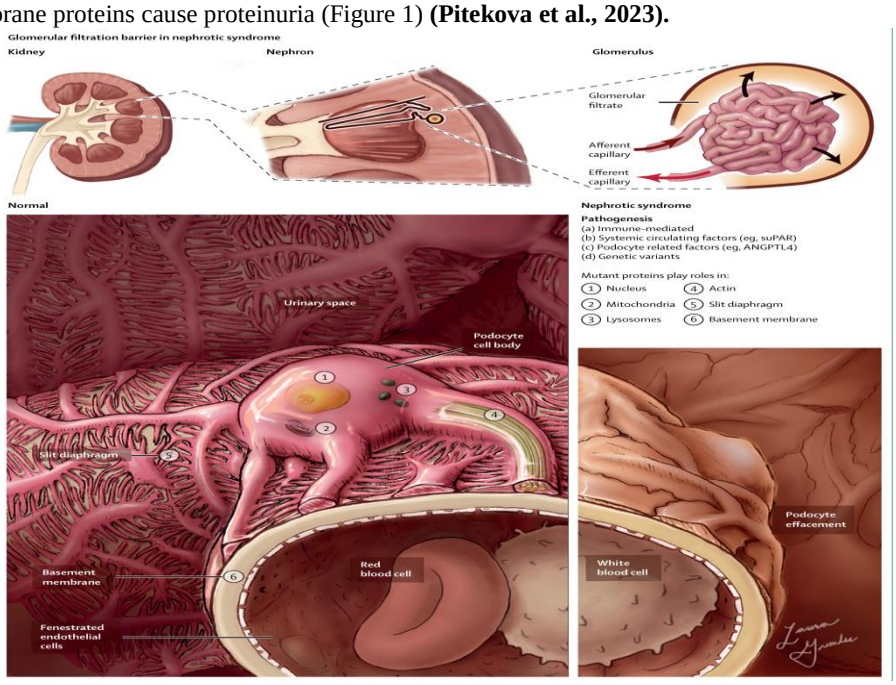

Figure (1): The glomerular filtration barrier consists of podocytes, basement membrane, and fenestrated endothelium. In nephrotic syndrome, podocyte effacement disrupts this barrier, causing albuminuria. Pathogenesis involves immune-mediated mechanisms or genetic variants. Mutations in nephrin, podocin, CD2AP, or actin-regulating proteins such as α-actinin 4 and INF2 impair podocyte integrity, leading to steroid resistance and focal segmental glomerulosclerosis (FSGS) (Noone, et al. 2018).

Immune Mechanisms
T-cell dysfunction is suggested by immunosuppressive response, remission after measles, and NS resolution after lymphoma treatment. Podocyte CD80 (B7-1) expression has been linked to proteinuria; abatacept/belatacept trials remain inconclusive **(Hackl et al., 2021).**

Circulating Factors
Evidence supports permeability factors in FSGS and SRNS, with candidate molecules including heparanase, hemopexin, suPAR, and ANGPTL4 variants **(Queirós et al., 2020).**

GENETICS

Steroid-Sensitive NS (SSNS)
SNPs in HLA-DQA1/DQB1 on chromosome 6p explain 4.6% of SSNS risk, with MHC polymorphisms repeatedly linked **(Dufek-Kamperis et al., 2020).**

Steroid-Resistant NS (SRNS)
Genetic testing helps stop futile immunosuppression and guide transplant planning. Monogenic causes account for 69–85% of NS in <3 months, 50–66% at 4–12 months, ~25% at 1–6 years, 18% at 7–12 years, and 11% at 13–18 years. In >1-year-old SRNS patients (n=1340), ~14% had mutations. Over 30 genes are linked, including NPHS1, NPHS2, LAMB2, WT1. Mitochondrial CoQ10 deficiency accounts for ~1% of familial SRNS, treatable with supplementation **(Gbadegesin et al., 2022).**

COMPLICATIONS

Infection
IgG and complement loss increase infection risk. Spontaneous bacterial peritonitis, usually from *S. pneumoniae*, occurs when albumin <3 g/dL. Pneumococcal vaccine and, in select cases, antibiotic prophylaxis are recommended **(Machungo et al., 2023; Trautmann et al., 2020).** Varicella poses risk; vaccination is safe in remission/low steroids, with VZIG and acyclovir after exposure **(Trautmann et al., 2020).**

Venous Thromboembolism
VTE occurs in ~3% of children, including cerebral, pulmonary, and renal vein thrombosis **(Shaker et al., 2025)**. Mechanisms involve prothrombotic factors, anticoagulant loss, and volume depletion. LMWH is standard, but routine prophylaxis is not advised **(Parker et al., 2023).**

Acute Kidney Injury
AKI complicates ~59% of hospitalized NS cases, linked to infection, nephrotoxic drugs, and SRNS. Risks include diuretics with hypovolemia, renal vein thrombosis, sepsis, and NSAID-induced nephritis **(Menon et al., 2019).**

Dyslipidaemia
NS causes hypercholesterolemia, hypertriglyceridemia, and lipoprotein abnormalities. Long-term cardiovascular risk is unclear. Statins are not routinely recommended but may be used in children >10 years with severe dyslipidemia, with close monitoring **(Baek et al., 2022).**

Management of Edema
Edema results from albumin loss, reduced oncotic pressure, and fluid accumulation. Management is essential for symptom relief and prevention of complications **(Kallash and Mahan 2021).**

Cardiovascular Risk in Nephrotic Syndrome
Patients with nephrotic syndrome (NS) face increased cardiovascular disease (CVD) risk due to hyperlipidemia, thrombogenesis, and endothelial dysfunction. Hypercholesterolemia is closely linked to hypoalbuminemia, while persistent proteinuria and renal insufficiency further heighten CVD risk. Children with minimal change nephrotic syndrome (MCNS) who respond to corticosteroids usually have transient hyperlipidemia and lower risk. In contrast, those with persistent proteinuria and hypoalbuminemia face early atherosclerosis from prolonged nephrotic hyperlipidemia **(Kulkarni et al., 2019).**

Lipid Abnormalities and Renal Impact
Frequently relapsing NS is associated with elevated VLDL, LDL, and lipoprotein (a), all contributors to atherosclerosis and glomerular damage. Lipid-induced endothelial injury causes lipoprotein accumulation in the mesangium, proliferation, and sclerosis **(Hari et al., 2020).**

Lipid-Lowering Therapy
HMG-CoA reductase inhibitors (statins) show potential benefit, with Prescott et al. demonstrating that reducing cholesterol in childhood may prevent future atherosclerosis. However, safety concerns exist, as adverse effects like myalgia and malaise have been reported in hypoalbuminemic children, even with standard doses. Thus, further prospective trials are required to confirm long-term safety and efficacy **(Rasslan Abd Elaziz et al. 2019).**

Cardiac Remodeling in NS
Nephrotic syndrome, characterized by proteinuria, hypoalbuminemia, hyperlipidemia, and edema, causes metabolic and

nutritional derangements with cardiovascular consequences **(Rasslan Abd Elaziz et al. 2019).**

Inflammation and Cardiac Dysfunction
Massive proteinuria leads to hypoproteinemia, edema, and malnutrition. Inflammatory cytokines, especially TNF-α and IL-1β, are elevated in plasma and urine of NS patients and in animal models. TNF-α impairs cardiomyocyte contractility and promotes heart failure, as shown in transgenic mice with TNF-α overexpression. While dyslipidemia and hypercoagulability contribute to CVD, studies suggest serum lipids do not fully explain endothelial dysfunction, and proteinuria itself is strongly linked to cardiovascular mortality **(Saiki et al., 2023).**

Cardiac Atrophy and Functional Impairment
Animal models, particularly puromycin aminonucleoside (PAN) nephrosis, show cardiac and skeletal muscle atrophy. PAN rats exhibited reduced protein/DNA ratio in skeletal muscle, reflecting impaired protein synthesis. Cardiac atrophy occurred without significant cardiomyocyte loss, and myosin heavy chain (MHC) expression was downregulated early. Despite normal systolic and diastolic function at rest, isoproterenol stress revealed impaired cardiac reserve. Renal sodium handling was also abnormal, with early retention and later excessive excretion despite persistent proteinuria **(Xiao et al., 2022).**

Molecular Mechanisms of Remodeling
Cardiac remodeling involves impaired calcium handling. SERCA2a expression is reduced, while its inhibitor phospholamban (PLB) is increased, leading to defective calcium kinetics. BNP levels are elevated in NS patients and PAN models, correlating with edema and sodium retention. Inflammatory cytokines, including TNF-α and IL-1β, further enhance BNP expression in cardiomyocytes, linking inflammation to dysfunction **(Nalcacioglu et al., 2020).**

Clinical Implications and Therapy
Recognizing cardiac involvement in NS is crucial. Management should address renal disease, dyslipidemia, malnutrition, and cardiovascular risk. TNF-α inhibitors show promise in reducing systemic inflammation and improving outcomes in NS. Early recognition and intervention in cardiac dysfunction may lower cardiovascular morbidity and mortality **(Lella et al., 2023).**

AORTIC ROOT DILATATION

Definition
The aortic root, comprising the annulus, sinuses of Valsalva, sinotubular junction, and ascending aorta, enlarges abnormally in aortic root dilatation. Normal dimensions vary by age, height, and weight, so body surface area–adjusted nomograms are required for assessment **(Jahanyar et al., 2024).**

Aneurysms
True aneurysms involve all three arterial wall layers—intima, media, adventitia—commonly due to atherosclerosis, medial degeneration, or dissection. Pseudoaneurysms result from full-thickness wall defects, usually after trauma or infection, with extravasated blood contained by soft tissues **(Bossone and Eagle 2021).**

Etiology
Causes include congenital, degenerative, mechanical, inflammatory, and infectious disorders **(Kurupati et al., 2025)**. The aortic wall has three layers: intima, media, and adventitia. Cystic medial necrosis, marked by elastic fiber loss, smooth muscle degeneration, and ground substance deposition, predisposes to aneurysm **(Harky et al. 2021).**

Cystic Medial Necrosis and Syndromes
Marfan syndrome is the prototype, but other conditions also show medial necrosis **(Allanson et al., 2021; Rodrigues Bento et al., 2022):**

- Bicuspid aortic valve (1–2% of population), often with dilatation
- Familial thoracic aortic aneurysms
- Turner and Noonan syndromes
- Ehlers-Danlos type IV, coarctation of the aorta, polycystic kidney disease
  Age and hypertension also accelerate degeneration.

Atherosclerotic and Traumatic Aneurysms
Ascending aortic atherosclerotic aneurysms have declined due to better hypertension and lipid control. Atherosclerosis causes intimal thickening, calcification, and wall ischemia, predisposing to aneurysm and dissection. Traumatic aneurysms often follow motor vehicle accidents, typically distal to the left subclavian artery, but may also occur at the root, arch, or after surgery/catheterization **(Bossone and Eagle 2021).**

Inflammatory and Infectious Aneurysms
Inflammatory aortitis occurs in Takayasu arteritis, giant cell arteritis, and HLA-B27 spondyloarthropathies. Mycotic aneurysms develop when bacteria seed damaged intima. Historically, syphilitic aortitis was the main cause, now rare with antibiotics **(Virmani et al., 2022).**

DIAGNOSIS OF AORTIC ROOT ANEURYSM

Clinical Presentation

Thoracic aortic aneurysms may cause chest pain, back pain, and dyspnea. Dissection may lead to hemorrhage and tamponade, annular dilatation to aortic insufficiency and heart failure, and thrombi to embolic events such as stroke. Inflammatory and infectious cases may present with fever, night sweats, malaise, rash, or ischemic symptoms **(Willerson and Buja 2020).**

Physical Examination

Findings depend on etiology. Marfan syndrome shows tall stature, arachnodactyly, and pectus deformities. Bicuspid valve may produce systolic ejection clicks or murmurs. Family history is crucial, as many aneurysms are first diagnosed in relatives **(Thakker and Braverman 2021).**

Imaging

- **Radiography**: may show mediastinal widening, enlarged knob, or tracheal shift **(Virmani et al. 2022).**
- **MRI and MDRCT**: preferred for precise imaging, valve assessment, and vascular measurement
- **Aortography**: invasive, maps aneurysm location and insufficiency, but contraindicated in renal insufficiency
- **Echocardiography**: TTE assesses proximal aorta and bicuspid valve, TOE provides high-resolution imaging of the arch. Tethering of aortic leaflets, due to sinotubular/annulus mismatch, predicts functional regurgitation and guides valve-sparing surgery (Figure 2)
- **Sonography**: accurate noninvasive diameter measurement with inner-edge technique **(Lemaire and Vancraeynest 2023).**

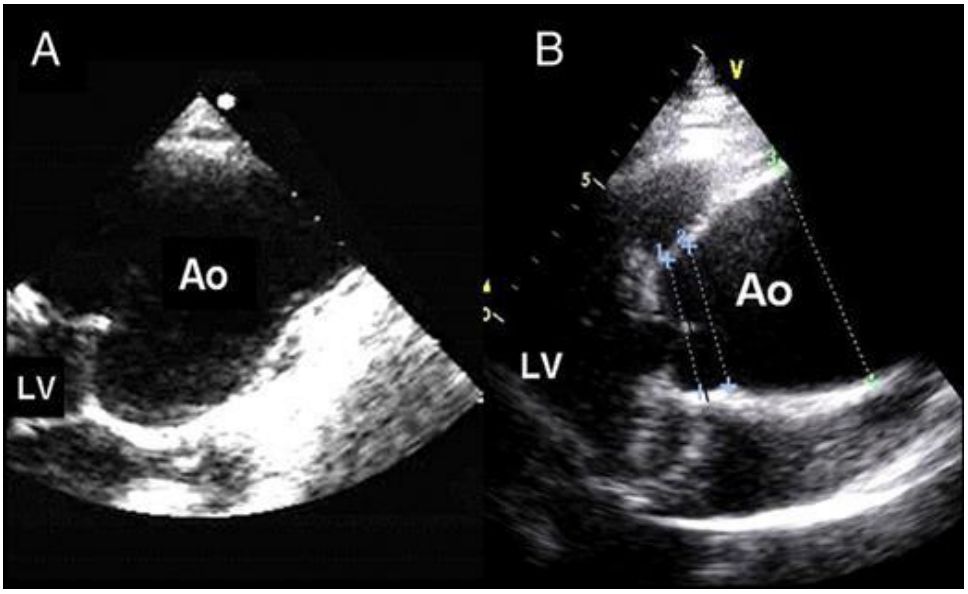

Figure (2): long-axis view by transthoracic echocardiography. (*A*) Annuloaortic ectasia with pyriform morphology. (*B*) Ascending aorta aneurysm located in the upper part of the sinotubular junction (Evangelista et al., 2019).

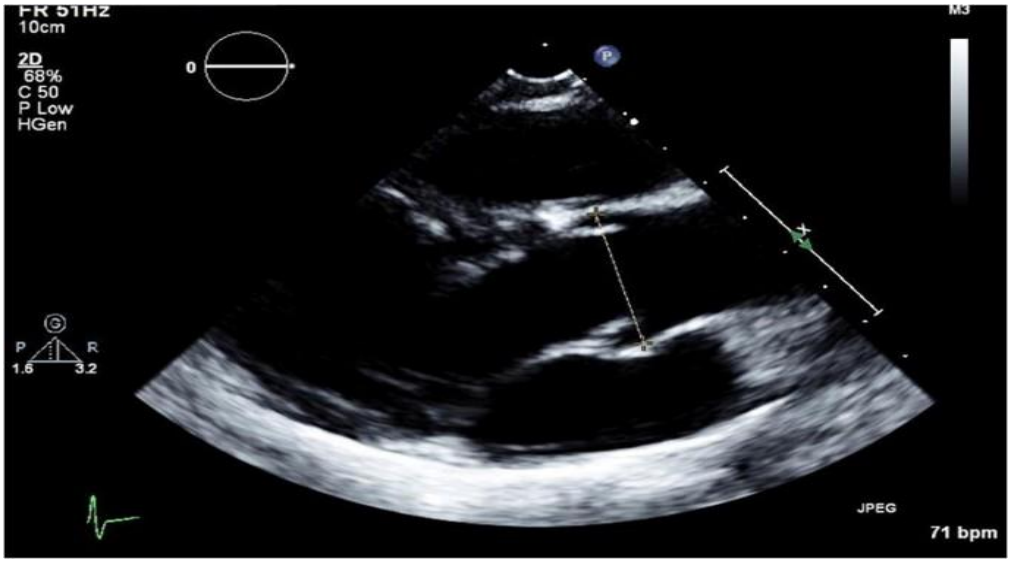

Figure (3): Inner edge to inner edge technique at end-systole for assessment of the aortic root (Madueme et al., 2020)

AORTIC DILATATION IN CHILDREN WITH KIDNEY DISEASE

Prevalence

In children on dialysis or post-transplant, proximal aortic dilatation prevalence is 31%, compared to 6% in milder CKD. In the general pediatric population, z-scores >2 occur in 2.3%. In primary uncontrolled hypertension, prevalence is 2.8%. In CKD, prevalence reaches 30.9% in those on renal replacement therapy **(Madueme et al., 2020).**

Mechanisms

Contributors include hypertension, fluid overload, chronic inflammation and uremic toxins, mineral metabolism disorders with vascular calcification **(Schmitt and Shroff 2023),** endothelial dysfunction, genetic predisposition such as Marfan or Loeys-Dietz, malnutrition and protein-energy wasting, and altered hemodynamics with shear stress **(Kim et al., 2022).**

Cardiovascular Implications

Aortic dilatation in CKD heightens risk of dissection, especially with uncontrolled hypertension, and can cause significant morbidity and mortality in children **(Quennelle et al. 2021).**

CONCLUSION

Aortic root dilatation represents an underrecognized but clinically significant complication in children with idiopathic nephrotic syndrome. Its pathogenesis is multifactorial, involving hemodynamic stress, inflammatory cytokines, endothelial dysfunction, metabolic derangements, and genetic predispositions. Compared with the general pediatric population, children with CKD and nephrotic syndrome exhibit markedly higher prevalence rates, especially those on renal replacement therapy. Given the risks of dissection, aneurysm, and rupture, routine cardiovascular surveillance—particularly echocardiographic screening with z-score–adjusted measurements—is warranted in high-risk patients. Future studies should clarify the prognostic value of aortic root changes, evaluate targeted therapies, and establish standardized monitoring guidelines. Comprehensive care that addresses both renal and cardiovascular complications is crucial to improving outcomes in this vulnerable population.

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