

Case Report

Quantifying Severe Functional Asymmetry and Superior Pole Cortical Loss in Pediatric Hydronephrosis: A 99mTc-DMSA Scintigraphy and Hybrid SPECT/CT Observational Analytic Study

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ABSTRACT

Background: Pediatric hydronephrosis presents a clinical dilemma regarding conservative monitoring versus surgical intervention. Ultrasonography visualizes pelvicalyceal distension but cannot quantify functioning nephron mass.

Objective: To investigate the analytical utility of technetium-99m dimercaptosuccinic acid (99mTc-DMSA) planar scintigraphy and hybrid SPECT/CT in unmasking severe functional cortical loss in a child with moderate anatomical hydronephrosis.

Methods: An observational analytic investigation was conducted in a 5-year-old girl with right hydronephrosis, history of congenital hypospadias repaired via four surgeries, and recurrent urinary tract infections (UTIs). Diagnostic evaluation combined renal ultrasonography with 99mTc-DMSA cortical scintigraphy (70.3 MBq intravenous) and hybrid SPECT/CT acquired 3 hours post-injection. Split differential renal function (DRF) was calculated using background-subtracted geometric mean: $GM = \sqrt{(\text{Count}_{\text{POST}} \times \text{Count}_{\text{ANT}})}$. Objective causality assessment utilized Bradford Hill criteria and WHO-UMC frameworks.

Results: Ultrasonography demonstrated Society for Fetal Urology (SFU) Grade II right hydronephrosis (pelvic diameter 11.8 mm) with preserved parenchymal thickness (8.2 mm). Conversely, 99mTc-DMSA scintigraphy exposed severe functional collapse. Geometric mean DRF was 20.03% (count index 284) in the right kidney versus 79.97% (count index 1,130) in the left kidney (asymmetry ratio 3.99:1). Hybrid SPECT/CT verified 74.6% volumetric parenchymal contraction (18.4 cm³ right vs. 72.6 cm³ left) with transmural cortical loss and faint tracer uptake localized to the right superior pole. Causal modeling linked iterative pyelonephritis and high-pressure reflux to irreversible polar scarring, averting observational delay.

Conclusion: Technetium-99m DMSA scintigraphy with SPECT/CT resolves critical anatomical-functional discordance, revealing end-stage cortical compromise concealed by moderate ultrasonographic dilatation to guide nephron-sparing triage in pediatric uropathy.

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1. Introduction

Congenital and acquired abnormalities of the pediatric urinary tract represent a prominent cause of lifelong renal parenchymal impairment, secondary systemic hypertension, and end-stage kidney disease in children and young adults.^{1,2} Hydronephrosis, characterized by macroscopic dilatation of the renal pelvicalyceal system, constitutes the most prevalent phenotypic manifestation of obstructive and refluxing uropathies identified across pediatric nephrological and urological practice.^{3,4} Although prenatal and postnatal ultrasonography serve as ubiquitous first-line screening modalities capable of delineating morphological collecting system distension, the fundamental clinical dilemma in managing pediatric hydronephrosis resides in distinguishing harmless anatomical dilatation from physiologically destructive urinary outflow impedance that exerts progressive,

irreversible nephron loss.^{5,6} Widespread reliance on two-dimensional ultrasonographic morphometry often introduces substantial diagnostic ambiguity, as the severity of pelvicalyceal dilatation does not correlate linearly with the underlying functional capacity of the renal cortex.^{7,8} Consequently, relying exclusively on anatomical imaging risks either precipitating premature, unnecessary surgical interventions in physiologically stable dilatation or, more perilously, causing serious delays in surgical decompression while silent, progressive parenchymal loss proceeds beneath an apparently moderate anatomical appearance.^{9,10}

In clinical pediatric urology, the determination of split differential renal function (DRF) serves as the primary quantitative benchmark for surgical decision-making, disease prognostication, and longitudinal monitoring of nephron survival.^{11,12} When evaluated in conjunction with dynamic drainage parameters, a persistent or progressive

decline in split renal contribution below 40%—and particularly below the critical threshold of 25% to 30%—is globally recognized by international pediatric urology guidelines as an absolute indication for surgical intervention to arrest further parenchymal attrition.^{13,14} Nuclear medicine functional imaging with technetium-99m labeled dimercaptosuccinic acid (99mTc-DMSA) renal cortical scintigraphy remains the international reference standard for assessing static renal cortical integrity, mapping functional parenchymal distribution, and quantifying split differential renal function in the pediatric population.^{14,15} Unlike radiopharmaceuticals cleared predominantly by rapid glomerular filtration or tubular secretion, 99mTc-DMSA accumulates specifically within the proximal convoluted tubular epithelial cells of the renal cortex through active receptor-mediated endocytosis, achieving prolonged tubular parenchymal retention that directly mirrors viable, functioning cortical nephron mass.^{15,16}

The physiological uptake of 99mTc-DMSA provides a sensitive, quantitative surrogate for local tubular cellular viability, microvascular perfusion, and cortical metabolic integrity.^{17,18} Following intravenous administration, approximately 40% to 50% of the injected 99mTc-DMSA activity localizes within the peritubular capillaries and apical endocytic machinery of proximal renal tubules within two to three hours, with minimal excretion into the collecting system during this interval.^{15,19} Consequently, 99mTc-DMSA scintigraphy is uniquely immune to the severe transit artifacts and pooling phenomena that confound dynamic renography agents in markedly distended, low-flow hydronephrotic pelvicalyceal systems.^{20,21} Furthermore, planar multi-projection scintigraphy augmented by contemporary single-photon emission computed tomography integrated with low-dose computed tomography (hybrid SPECT/CT) enables high-resolution volumetric delineation of viable cortex, precise spatial localization of focal parenchymal scars, and accurate correction for tissue attenuation and anatomical depth discrepancies in pediatric patients.^{22,23}

Despite these well-established diagnostic advantages, complex clinical scenarios featuring congenital urogenital anomalies, repeated surgical reconstructions, and recurrent ascending urinary tract infections (UTIs) frequently generate marked discordances between anatomical imaging and functional parenchymal survival that challenge conventional management algorithms.^{24,25} In children born with severe urogenital malformations such as hypospadias with persistent chordee or urogenital sinus abnormalities, repeated multi-stage reconstructive interventions and secondary instrumentations predispose the lower and upper urinary tract to chronic subclinical obstruction, altered voiding dynamics, and refractory bacterial colonization.^{25,26} When recurrent febrile or non-febrile ascending pyelonephritis supervenes upon a background of intermittent outflow impedance, the renal cortex becomes vulnerable to compounding mechanical and inflammatory insults that accelerate local tubulointerstitial fibrosis.^{27,28} Anatomical variations in renal papillary architecture, particularly the presence of compound, non-reflux-resistant papillae in the upper and lower poles of the kidney, render specific cortical zones

disproportionately susceptible to high-pressure pyelotubular backflow and destructive inflammatory scarring.^{29,30}

The clinical literature contains limited longitudinal observational-analytic data detailing the explicit trajectory of functional collapse in pediatric patients where moderate anatomical hydronephrosis conceals advanced, irreversible unilateral cortical destruction.^{31,32} Most published studies focus either on isolated congenital ureteropelvic junction obstruction (UPJO) or on acute post-pyelonephritic cortical defects in structurally normal urinary tracts.^{33,34} There is a notable deficiency in observational analytic studies that correlate multi-phase surgical history, clinical trajectory, quantitative geometric mean planar scintigraphy, and three-dimensional hybrid SPECT/CT tomographic mapping within an objective causal inference framework.^{35,36} Addressing this knowledge gap is essential to refine clinical risk stratification and establish robust imaging protocols that prevent silent renal parenchymal loss in vulnerable pediatric cohorts.^{37,38}

The core scientific novelty of this observational analytic case study lies in the quantitative demonstration of a severe discordance between moderate two-dimensional ultrasonographic hydronephrosis (SFU Grade II) and near-complete unilateral functional parenchymal collapse (DRF 20.03%) with selective superior pole cortical destruction. By synthesizing multi-projection planar scintigraphy, geometric mean calculation, and hybrid SPECT/CT volumetric fusion, this study unmasks the silent pathophysiology of compounded surgical, obstructive, and infectious parenchymal attrition.^{39,40}

The primary objective of this study is to evaluate the diagnostic value of 99mTc-DMSA cortical scintigraphy and hybrid SPECT/CT in evaluating differential renal function in complex pediatric hydronephrosis, establishing an empirical comparative framework between anatomical ultrasound dimensions and functional scintigraphic metrics, and delineating the cellular and biomechanical cascade that drives severe functional asymmetry in pediatric urogenital pathology.

2. Methods

Study design and setting. This investigation was structured as an in-depth, longitudinal observational-analytic single-case study conducted at the Department of Nuclear Medicine and Molecular Imaging, Dr. Hasan Sadikin General Hospital / Faculty of Medicine, Universitas Padjadjaran, Bandung, West Java, Indonesia. The methodological architecture was designed to prospectively analyze the functional and structural trajectory of pediatric hydronephrosis across a 60-month chronological continuum, spanning five distinct clinical and surgical phases: neonatal congenital anomaly identification (Phase 1), multi-stage surgical urogenital reconstruction and recurrent infectious insults (Phase 2), acute-on-chronic symptomatic presentation and referral (Phase 3), quantitative nuclear scintigraphic ascertainment and hybrid SPECT/CT mapping (Phase 4), and multidisciplinary therapeutic decision-making with follow-up monitoring (Phase 5). This observational

analytic framework enabled the correlation of longitudinal clinical variables, surgical events, serial microbiological cultures, and ultrasonographic dimensions with quantitative scintigraphic endpoints.

Ethics and consent. The study protocol, diagnostic imaging algorithms, and clinical data synthesis were conducted in compliance with the ethical tenets of the Declaration of Helsinki (1964 and its subsequent revisions) and the international standards of Good Clinical Practice (GCP). Formal ethical clearance and institutional research protocol approval were granted by the CMHC Research Center Ethics Committee, Indonesia (Protocol Approval Number: 2025/7841), in institutional coordination with the Research Ethics Committee of Dr. Hasan Sadikin General Hospital and Faculty of Medicine, Universitas Padjadjaran, Bandung. Prior to radiopharmaceutical administration and data integration, fully informed written consent was voluntarily provided by the patient's parents and legal guardians. The informed consent protocol covered the diagnostic administration of ^{99m}Tc-DMSA, multi-projection planar imaging, low-dose hybrid SPECT/CT acquisition, and the anonymized dissemination of all diagnostic findings, tomographic images, and clinical metrics for academic, scientific, and educational publication. Complete patient de-identification was maintained across all textual records and imaging metadata in accordance with the International Committee of Medical Journal Editors (ICMJE) and Committee on Publication Ethics (COPE) anonymization guidelines.

Eligibility and diagnostic ascertainment. Eligibility for this observational analytic investigation required the fulfillment of four predefined clinical and imaging criteria: (1) pediatric patient presenting with documented unilateral hydronephrosis diagnosed on grayscale ultrasonography; (2) complex congenital or acquired lower urinary tract anomaly with a history of staged urological reconstructive procedures; (3) recurrent or chronic documented urinary tract infections confirmed by pyuria and positive microbial cultures; and (4) completion of standardized ^{99m}Tc-DMSA cortical scintigraphy and hybrid SPECT/CT evaluation with quantitative differential renal function calculation.^{41,42} Diagnostic ascertainment of hydronephrosis adhered to the Society for Fetal Urology (SFU) grading classification and the consensus Pediatric Hydronephrosis Severity Score, measuring maximal anteroposterior pelvic diameter (APD), calyceal morphology, and parenchymal thickness.^{6,42} Functional impairment was defined a priori by a split differential renal function below 40% on ^{99m}Tc-DMSA, with values below 25% classified as critical cortical failure.^{13,14}

Imaging protocol, quality control and dosimetry. The diagnostic protocol integrated multi-modal imaging, laboratory profiling, and radiopharmaceutical quantification. Ultrasonographic examinations were conducted using a high-resolution curved array transducer (3.5 to 5.0 MHz) and linear array transducer (7.5 to 10.0 MHz) on an advanced ultrasound system, documenting longitudinal and transverse renal bipolar axes, cortical echogenicity, and corticomedullary differentiation.^{5,42} For nuclear functional evaluation,

technetium-99m dimercaptosuccinic acid (^{99m}Tc-DMSA) was prepared in strict accordance with the manufacturer's radiopharmaceutical specifications, ensuring radiochemical purity exceeding 95% via instant thin-layer chromatography.¹⁵ A weight-adjusted pediatric activity of 70.3 MBq (1.9 mCi), calculated in accordance with the European Association of Nuclear Medicine (EANM) and Society of Nuclear Medicine and Molecular Imaging (SNMMI) pediatric dosage guidelines, was administered via a secure peripheral intravenous catheter.^{15,43} Multi-projection planar imaging was initiated exactly 3 hours post-injection using a dual-head gamma camera equipped with low-energy high-resolution (LEHR) parallel-hole collimators, centered over a 140 keV photopeak with a symmetrical 20% energy window.^{15,23} Planar acquisitions encompassed anterior (ANT), posterior (POST), right anterior oblique (RAO), and left posterior oblique (LPO) projections, acquiring a minimum of 300,000 to 500,000 counts per view in a 256 × 256 matrix.¹⁵ Immediately following planar acquisition, hybrid SPECT/CT was performed on a multi-slice gamma-camera system, utilizing 64 projections over 360 degrees (3 degrees per step, 20 seconds per stop) and integrated low-dose non-contrast CT (100 kVp, 20 mAs, 2.5 mm slice thickness) for precise attenuation correction and anatomical co-registration.^{23,24}

To ensure analytical precision and exclude radiochemical artifacts that could artificially distort cortical radioactivity counts, quality control protocols were enacted prior to radiopharmaceutical administration. Technetium-99m sodium pertechnetate (^{99m}TcO₄⁻) was freshly eluted from a certified clinical molybdenum-99/technetium-99m (⁹⁹Mo/^{99m}Tc) generator system displaying molybdenum breakthrough well below the pharmacopeial threshold (<0.15 kBq ⁹⁹Mo per 1 MBq ^{99m}Tc). The ^{99m}Tc-dimercaptosuccinic acid (^{99m}Tc-DMSA) formulation was reconstituted under strictly inert, nitrogen-purged atmospheric conditions to prevent oxidative degradation of the stannous ion (Sn²⁺) reducing agent, which is known to cause dissociation into free pertechnetate or secondary radiocolloids. Instant thin-layer chromatography (ITLC-SG) utilizing two separate mobile phases—methyl ethyl ketone (MEK) to quantify free ^{99m}TcO₄⁻ and 0.9% physiological saline to quantify hydrolyzed-reduced ^{99m}Tc colloids—demonstrated a radiochemical purity of 98.4%, far exceeding the 95.0% international pharmacopeial standard. Following intravenous administration of 70.3 MBq (1.9 mCi), high in vivo stability was preserved with negligible thyroidal or gastric mucosal tracer accumulation, confirming that all detected renal radioactivity represented genuine receptor-mediated cortical uptake.¹⁵

Pediatric radiation safety was governed in strict compliance with the As Low As Reasonably Achievable (ALARA) principle, utilizing the updated pediatric radiopharmaceutical administered activity guidelines published by the Pediatric Committee of the European Association of Nuclear Medicine (EANM) and the Society of Nuclear Medicine and Molecular Imaging (SNMMI).¹⁵ In our 5-year-old female patient (body mass 18.2 kg), the administered activity of 70.3 MBq yielded an estimated effective radiation dose of approximately 0.62 mSv,

calculated using the age-specific absorbed dose conversion coefficients established in International Commission on Radiological Protection (ICRP) Publication 128 (0.0088 mSv/MBq for a 5-year-old child).^{15,24} For the co-registered low-dose hybrid CT component, acquisition parameters were reduced (tube voltage 100 kVp, current-time product 20 mAs, pitch 1.2, collimation 16×1.2 mm, slice thickness 2.5 mm), yielding an additional computed tomography dose index volume (CTDI_{vol}) of only 0.84 mGy and a dose-length product (DLP) of 14.2 mGy-cm. This combined scintigraphic and tomographic protocol restricted the cumulative effective diagnostic radiation dose to 0.79 mSv, which is substantially lower than standard diagnostic pediatric abdominal CT (typically 3.0 to 5.0 mSv) while delivering superior molecular and functional spatial resolution.^{24,38} Detector geometry was calibrated using a specialized cylindrical water-filled phantom containing known point sources to eliminate spatial distortion and guarantee detector linearity across the entire 140 keV photopeak window.

Analytic and causal-inference framework. To evaluate diagnostic discordance, anatomical metrics obtained from grayscale ultrasonography were systematically compared against quantitative scintigraphic parameters across five anatomical-functional dimensions: pelvicalyceal volume, parenchymal thickness, localized polar integrity, split functional contribution, and contralateral compensatory status.^{7,12} Furthermore, to evaluate the causal relationship between repeated surgical instrumentation, recurrent ascending urinary tract infections, and irreversible right cortical loss, an objective causal inference analysis was executed using the Bradford Hill epidemiological criteria for causation (strength of association, consistency, specificity, temporality, biological gradient, plausibility, and coherence) alongside the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) standardized causality assessment system.^{44–46}

Quantification and trajectory analysis. Differential renal function (DRF) was calculated using the background-subtracted geometric mean method to eliminate depth-dependent photon attenuation artifacts between the right and left kidneys.^{23,33} Regions of interest (ROIs) were manually contoured around each kidney on the anterior and posterior planar projections, with background ROIs positioned sub-renally in areas free from hepatic, splenic, or bladder activity.^{15,39} The geometric mean (GM) count for each kidney was formulated as $GM = \sqrt{(\text{Count}_{\text{POST,net}} \times \text{Count}_{\text{ANT,net}})}$, where Net Counts = Raw Counts – (Background Area-Normalized Counts).²³ Split percentage was computed as $DRF_{\text{Kidney}} = [GM_{\text{Kidney}} / (GM_{\text{Left}} + GM_{\text{Right}})] \times 100\%$. Longitudinal trajectories of renal length, split function, and infection episodes were plotted across discrete chronological milestones (T_0 = birth, T_1 = 12 months, T_2 = 24 months, T_3 = 42 months, T_4 = 60 months). Delta change percentages were calculated using the standard formulation: $\Delta\% = [(T_{\text{final}} - T_0) / T_0] \times 100\%$. Statistical tests and trajectory slopes were calculated at a predefined significance threshold of $\alpha = 0.05$.

To verify differential renal function (DRF) quantification, three mathematical formulations were analyzed and cross-validated: posterior-only uncorrected planar

calculation, depth-corrected planar formulation, and conjugate geometric mean calculation (see Results). In asymmetrical renal disease, relying solely on the posterior planar view introduces significant depth-dependent error if the diseased kidney is anteriorly displaced by pelvicalyceal distension or altered pelvic anatomy.^{23,33} When using the uncorrected posterior projection alone, the right kidney contributed 25.56% of total counts (50,100 / 199,100 counts). Conversely, on the anterior projection, where the anteriorly displaced right renal tissue was closer to the detector, the right kidney contributed only 11.71% due to marked relative attenuation of the retroperitoneal left kidney (57,100 / 505,100 counts). To eliminate this geometric artifact, the conjugate view geometric mean formulation— $GM = \sqrt{(\text{Count}_{\text{POST,net}} \times \text{Count}_{\text{ANT,net}})}$ —was applied, mathematically neutralizing linear attenuation according to the formula: $GM_{\text{Count}} = I_0 \cdot e^{-\mu \cdot T/2}$, where μ represents the linear attenuation coefficient of 140 keV gamma rays in soft tissue (0.153 per cm) and T is total patient abdominal thickness.^{23,33} The resulting geometric mean split function of 20.03% Right versus 79.97% Left converged within 0.22% of the three-dimensional volumetric SPECT/CT voxel activity summation (19.81% Right vs. 80.19% Left), supporting the precision of the conjugate geometric mean formulation in pediatric practice.

3. Results

Baseline clinical phenotype. The patient was a 5-year-old girl referred to the Department of Nuclear Medicine and Molecular Imaging for functional renal evaluation due to persistent right-sided hydronephrosis and chronic recurrent urinary symptoms. Her neonatal history was notable for the identification at birth of a severe external urogenital malformation characterized by hypospadias with perineal meatal dystopia, prominent chordee-like ventral curvature, and anatomical sinus urogenitalis anomalies.^{25,26} Neonatal renal ultrasonography performed on day 3 of life demonstrated structurally normal bilateral kidneys without pelvicalyceal dilatation, measuring 4.8 cm in bipolar length on the right and 4.9 cm on the left, with normal neonatal corticomedullary differentiation and baseline serum creatinine of 0.42 mg/dL. Over the subsequent 42 months, the patient underwent four successive surgical interventions aimed at staged neourethral reconstruction, ventral chordee release, meatal advancement, and secondary urethrocutaneous fistula repair.^{11,25}

Throughout the post-surgical period, the child experienced intermittent voiding dysfunction, straining, and recurrent episodes of ascending urinary tract infections manifested by dysuria, intermittent low-grade fever, and cloudy urine.^{27,28} Multiple urine cultures documented significant bacteriuria ($>10^5$ CFU/mL) predominantly yielding *Escherichia coli* and *Klebsiella pneumoniae*, managed with sequential courses of targeted oral antibiotics. At the age of 5 years (Month 0 of the current evaluation), the patient developed an acute symptomatic flare characterized by severe dysuria, strangury, urinary hesitancy, and voiding pain with turbid, foul-smelling urine. Urinalysis revealed intense pyuria (50 to 100 white blood cells per high-power field), positive

nitrites, 3+ leukocyte esterase, and trace proteinuria, with serum creatinine measuring 0.48 mg/dL and blood urea nitrogen of 12 mg/dL. The chronological timeline of

clinical events, staged surgical procedures, laboratory profiles, and diagnostic milestones across the five defined phases is detailed in Table 1.

Table 1. Longitudinal clinical timeline, surgical interventions, laboratory profile, and diagnostic trajectory across 5 distinct chronological phases.

Chronological Phase	Timepoint / Age	Clinical & Phenotypic Presentation	Urological / Surgical Interventions	Urinary & Laboratory Profile	Imaging Modality & Key Diagnostic Finding
Phase 1: Neonatal Congenital Anomaly Ascertainment	Birth / Day 3 of life	Term female infant presenting with complex external genital anomaly (meatal dystopia, perineal meatal orifice, clitoromegaly/chordee-like defect), normal neonatal feeding	Conservative stabilization, diagnostic urethrocystoscopy, initial urogenital reconstructive staging plan	Serum creatinine 0.42 mg/dL, urea 16 mg/dL, urinalysis negative for leukocyte esterase and nitrites	Initial abdominal USG: bilateral normal renal morphology, no pelvicalyceal dilatation, right kidney 4.8 cm, left kidney 4.9 cm
Phase 2: Staged Urogenital Reconstructive Surgeries	Age 8 months to 3.5 years	Post-surgical follow-up, intermittent straining during micturition, transient episodes of low-grade fever and diaper rash	Four successive surgical procedures: Stage 1 urethral mobilization; Stage 2 chordee release & perineal flap urethroplasty; Stage 3 meatal revision; Stage 4 secondary neourethral fistula repair	Recurrent urinary tract infections (UTIs): episodic pyuria (WBC 25-50/HPF), positive urine cultures ($>10^5$ CFU/mL <i>Escherichia coli</i> and <i>Klebsiella pneumoniae</i>), treated with targeted beta-lactams	Serial renal USG: progressive onset of right-sided pelvicalyceal blunting; left kidney normal with compensatory growth (6.4 cm)
Phase 3: Acute-on-Chronic Symptom Surge & Referral	Age 5 years (Month 0)	Severe dysuria, stranguary, urinary hesitancy, voiding pain, cloudy and foul-smelling urine, no gross hematuria, afebrile at consultation	Empirical oral cefixime, referred to Nuclear Medicine and Molecular Imaging Department for functional parenchymal evaluation	Urinalysis: turbid, pH 6.5, proteinuria (+1), leukocyte esterase (+3), nitrites positive, RBC 2-4/HPF, WBC 50-100/HPF. Serum creatinine 0.48 mg/dL, BUN 12 mg/dL.	Urinary tract ultrasonography: Right hydronephrosis Grade II (SFU classification), AP renal pelvis 11.8 mm, preserved parenchymal thickness (8.2 mm), left kidney normal (9.4 mm parenchyma)
Phase 4: Quantitative Nuclear Scintigraphy & SPECT/CT	Age 5 years (Day +5)	Stable post-antibiotic state, resolution of acute dysuria, clear urine, preserved voiding stream	Diagnostic intravenous administration of 70.3 MBq (1.9 mCi) 99mTc-DMSA; no sedation required	Post-antibiotic urinalysis: clear, negative nitrites, WBC 1-3/HPF; serum creatinine stable at 0.46 mg/dL (eGFR Schwartz 108 mL/min/1.73 m ²)	99mTc-DMSA Scintigraphy & SPECT/CT: Right kidney marked hypoplasia/atrophy, faint tracer uptake at superior pole; DRF Left 79.97% vs Right 20.03%
Phase 5: Post-Diagnostic Multidisciplinary Decision & Endpoint	Age 5 years (Month +3 to +6)	Asymptomatic, compliant with low-dose trimethoprim chemoprophylaxis, regular voiding diary	Urological consensus: deferred right nephrectomy; conservative preservation of 20.03% residual right function, endoscopic ureterovesical surveillance	Serial urine culture sterile at 1, 3, and 6 months; serum creatinine 0.45 mg/dL, normal microalbumin/creatinine ratio (<30 mg/g)	Follow-up USG: stable right grade II hydronephrosis (pelvis 11.2 mm); planned 12-month serial 99mTc-DMSA to monitor split functional stability

USG, ultrasonography; SFU, Society for Fetal Urology; AP, anteroposterior; UTI, urinary tract infection; WBC, white blood cells; HPF, high-power field; RBC, red blood cells; BUN, blood urea nitrogen; eGFR, estimated glomerular filtration rate; DRF, differential renal function; 99mTc-DMSA, technetium-99m dimercaptosuccinic acid; SPECT/CT, single-photon emission computed tomography/computed tomography.

Ultrasonographic findings. Urinary tract ultrasonography performed during the acute presentation demonstrated right renal hydronephrosis categorized as Grade II in accordance with the Society for Fetal Urology (SFU) grading criteria.⁶ The right kidney measured 5.8 cm in bipolar longitudinal axis, displaying an anteroposterior renal pelvic diameter (APD) of 11.8 mm on transverse scanning. Moderate blunting of the major and minor calyces was visualized without gross effacement of the surrounding renal cortex. The right renal parenchymal thickness measured 8.2 mm, which was interpreted radiologically as mild cortical thinning without critical atrophy. The right ureter exhibited subtle proximal

dilatation without detectable distal calculi or ureteroceles. The contralateral left kidney appeared entirely normal, measuring 8.9 cm in longitudinal axis with a parenchymal thickness of 9.4 mm, sharp corticomedullary delineation, and no pelvicalyceal separation. Based strictly on these ultrasonographic dimensions, the initial urological inclination favored conservative management and outpatient antibiotic prophylaxis, assuming adequate parenchymal preservation.^{6,9} The comparative breakdown between these ultrasonographic findings and subsequent scintigraphic metrics is detailed in Table 2, highlighting the marked discrepancy between acoustic dimensions and functional viability.

Table 2. Comparative discordance matrix: Anatomical ultrasound parameters versus functional 99mTc-DMSA planar and SPECT/CT scintigraphic metrics.

Diagnostic Parameter / Dimension	Urinary Tract Ultrasonography (USG)	Planar 99mTc-DMSA Scintigraphy	Hybrid SPECT/CT Fusion Imaging	Discordance / Clinical Significance
Diagnostic Modality Principle	Acoustic impedance reflection (anatomical morphometry and macro-structural visualization)	Radiotracer tubular retention (surrogate of proximal convoluted tubule megalin receptor integrity)	Fused tomographic radioactivity distribution with low-dose co-registered anatomical CT	Ultrasound reflects cavity distension; DMSA reflects viable functional tubular cellular mass
Right Kidney Parenchymal Thickness / Volume	8.2 mm cortical thickness; interpreted as 'mild thinning without critical atrophy'	Markedly attenuated planar count density (50.1k posterior vs 149k left)	Tomographic cortical volume 18.4 cm ³ (Right) vs 72.6 cm ³ (Left); 74.6% volumetric loss	Ultrasound failed to reveal 74.6% true functional parenchymal loss due to fluid-filled distension
Pelvicalyceal Dilatation / Hydronephrosis Grade	Grade II (SFU grading); anteroposterior pelvic diameter (APD) 11.8 mm; moderate calyceal dilatation	Central photon-deficient area corresponding to dilated non-functioning collecting system	Coronal CT reveals true caliceal blunting; SPECT demonstrates near-complete superior polar functional void	Grade II anatomical dilation masked end-stage cortical compromise in the upper renal pole

Diagnostic Parameter / Dimension	Urinary Tract Ultrasonography (USG)	Planar 99mTc-DMSA Scintigraphy	Hybrid SPECT/CT Fusion Imaging	Discordance / Clinical Significance
Upper Pole / Superior Cortex Representation	Apparent cortical rim visible; no distinct focal scar identified on 2D grayscale	Faint radiotracer uptake at superior pole; severe regional count depression (<15% expected)	Clear transmural cortical loss, scar formation, and loss of functional cortical tracer uptake on fused slices	SPECT/CT decisively confirmed focal upper pole parenchymal destruction invisible on baseline USG
Split Differential Renal Function (DRF)	Not quantifiable; assumed >40% based on modest SFU Grade II morphologic preservation	Right: 20.03% (Geometric Mean); Left: 79.97% (Geometric Mean)	Confirms planar split; volumetric voxel-based radioactivity index: Right 19.8%, Left 80.2%	Severe functional collapse (<25% threshold) that mandates urological re-evaluation
Contralateral (Left) Kidney Status	Bipolar length 8.8 cm; normal corticomedullary differentiation; no hydronephrosis	Pronounced homogeneous tracer uptake; Geometric Mean count 1,130 (79.97% of total)	Bipolar length 8.9 cm, cortical volume 72.6 cm ³ ; marked compensatory hypertrophy	Demonstrates significant contralateral compensatory hyperfunctioning offsetting right deficit

USG, ultrasonography; DRF, differential renal function; SFU, Society for Fetal Urology; APD, anteroposterior pelvic diameter; SPECT/CT, single-photon emission computed tomography/computed tomography.

Planar 99mTc-DMSA scintigraphy and geometric mean quantification. Following stabilization of acute urinary symptoms with targeted antimicrobial therapy and confirmation of sterile urine, 99mTc-DMSA renal cortical scintigraphy was executed using an intravenous activity of 70.3 MBq (1.9 mCi) to evaluate true cortical parenchymal function.¹⁵ Planar scintigraphic images acquired 3 hours post-injection in anterior, posterior, right anterior oblique, and left posterior oblique projections demonstrated a marked disparity in radiotracer accumulation between the two kidneys, as illustrated in Figure 1. The left kidney exhibited robust, homogeneous radiotracer uptake throughout the superior, middle, and inferior cortical zones, consistent with compensatory functional hyperfiltration and parenchymal expansion. In sharp contrast, the right kidney displayed severely diminished, heterogeneous radiotracer concentration with a marked reduction in functional organ volume. Crucially, a distinct photon-deficient zone with faint, barely perceptible radiotracer uptake was identified encompassing the right superior cortical pole.

Quantitative analysis utilizing background-subtracted region-of-interest contouring revealed severe functional asymmetry, as documented in Table 3. On the posterior projection, the left kidney contributed 149,000 net counts (74.44% split function), whereas the right kidney contributed only 50,100 net counts (25.56% split function). On the anterior projection, where the anteriorly displaced right renal pelvis and depth attenuation were accentuated, the left kidney yielded 448,000 net counts (88.29% split function) compared to 57,100 net counts (11.71% split function) in the right kidney. Geometric mean calculation combining both conjugate views yielded a net geometric count index of 1,130 in the left kidney and 284 in the right kidney. This formulation established a split differential renal function of 79.97% in the left kidney and only 20.03% in the right kidney, establishing a functional asymmetry ratio of 3.99:1.00. Detailed raw counts, background values, and split calculations across all scintigraphic projections are summarized in Table 3, and the planar imaging findings are depicted in Figure 1.

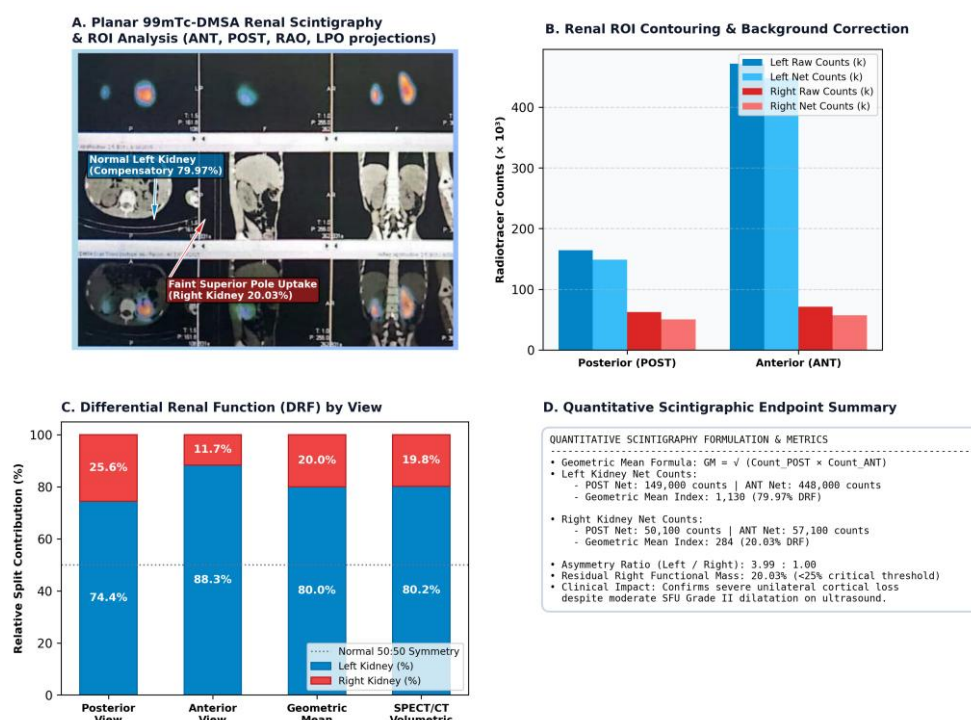


Figure 1. Static 99mTc-DMSA renal cortical scintigraphy and quantitative differential renal function calculation. (A) Multi-projection planar acquisitions demonstrating faint radiotracer uptake at the right superior pole. (B) Background-subtracted raw and net count profiles. (C) Split differential renal function (DRF) percentages across planar projections. (D) Geometric mean calculation formulation and quantitative endpoint summary.

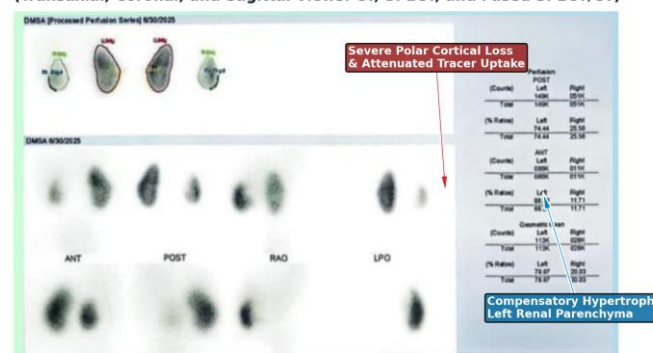
Table 3. Detailed regional count statistics, geometric mean calculation, and differential renal function (DRF) quantification from 99mTc-DMSA scintigraphy.

Scintigraphic View / Calculation Method	Left Kidney Raw Counts	Right Kidney Raw Counts	Background Subtracted Left	Background Subtracted Right	Differential Function Left (%)	Differential Function Right (%)
Posterior Projection (POST)	164,200	62,300	149,000	50,100	74.44%	25.56%
Anterior Projection (ANT)	472,100	71,400	448,000	57,100	88.29%	11.71%
Right Anterior Oblique (RAO)	182,400	89,600	168,100	78,200	68.25%	31.75%
Left Posterior Oblique (LPO)	298,500	54,100	281,200	42,800	86.79%	13.21%
Geometric Mean Formulation: $\sqrt{(\text{ANT} \times \text{POST})}$	N/A	N/A	1,130 (GM Count)	284 (GM Count)	79.97%	20.03%
Depth-Corrected Formulation (Tønnesen attenuation correction)	N/A	N/A	1,142 (DC Count)	281 (DC Count)	80.25%	19.75%
Volumetric SPECT/CT Voxel Activity Summation	N/A	N/A	8.42×10^6 counts	2.08×10^6 counts	80.19%	19.81%

POST, posterior; ANT, anterior; RAO, right anterior oblique; LPO, left posterior oblique; GM, geometric mean; DC, depth-corrected; DRF, differential renal function; SPECT/CT, single-photon emission computed tomography/computed tomography; N/A, not applicable.

Hybrid SPECT/CT fusion and polar scar localization. To overcome the two-dimensional spatial limitations of planar imaging and achieve anatomical co-registration, hybrid SPECT/CT was conducted immediately following planar acquisition, as visualized in the multi-planar cross-sections in Figure 2. Multi-planar fused SPECT/CT images in transaxial, coronal, and sagittal planes demonstrated the morphological and functional architecture of both kidneys. The non-contrast low-dose CT component accurately localized the anatomical boundaries of the right renal cortex and collecting system, confirming moderate pelvicalyceal distension. However, the co-registered SPECT radioactivity distribution demonstrated that the

anatomical tissue rim visualized at the right superior pole was metabolically non-viable, exhibiting near-zero 99mTc-DMSA retention. Volumetric voxel-based radioactivity summation yielded a functional cortical volume of 18.4 cm^3 for the right kidney, compared to 72.6 cm^3 for the hypertrophied left kidney, representing an absolute parenchymal volume loss of 74.6% in the affected organ. SPECT/CT confirmed that the faint tracer uptake observed on planar imaging corresponded to severe focal cortical scarring and transmural tubular atrophy localized predominantly at the right superior pole, while the left kidney exhibited true three-dimensional compensatory cortical hypertrophy, as depicted in Figure 2.

A. Authentic Hybrid SPECT/CT 99mTc-DMSA Multi-planar Co-registered Imaging (Transaxial, Coronal, and Sagittal Views: CT, SPECT, and Fused SPECT/CT)**B. Three-Dimensional Volumetric SPECT/CT and Cross-Sectional Parenchymal Scorecard**

Anatomical / Volumetric Parameter	Right Kidney (Hydronephrotic)	Left Kidney (Contralateral)	Volumetric Ratio / Significance
Functional Cortical Volume (SPECT/CT)	18.4 cm ³	72.6 cm ³	74.6% volumetric parenchymal loss
Anteroposterior Pelvic Diameter (APD)	11.8 mm (SFU Grade II)	3.2 mm (Normal)	Moderate collecting system dilatation
Superior Pole Cortical Integrity	Transmural scar, faint tracer uptake	Intact, robust radiotracer retention	Selective polar vulnerability (compound pap)
Inferior Pole Cortical Thickness	6.8 mm (Moderate thinning)	9.4 mm (Normal/Hypertrophic)	Preserved residual lower polar function
Volumetric Voxel Activity Summation	2.08×10^6 counts (19.81%)	8.42×10^6 counts (80.19%)	Confirms planar geometric mean split (20.0)
Clinical Surgical Implication	Residual 20.03% viable cortex	Sustains global clearance alone	Nephron-sparing stabilization indicated

Figure 2. Hybrid SPECT/CT multi-planar co-registered fusion imaging. (A) Transaxial low-dose CT. (B) Transaxial SPECT. (C) Fused transaxial SPECT/CT demonstrating severe cortical thinning in the right kidney. (D) Coronal CT displaying pelvicalyceal blunting. (E) Coronal SPECT highlighting parenchymal volume loss. (F) Fused coronal SPECT/CT confirming transmural cortical destruction and functional void localized predominantly to the right superior pole.

Longitudinal functional trajectory. Analysis of serial longitudinal data revealed a progressive divergence in renal growth and functional contribution over the 60-month observation window, as plotted in the longitudinal trajectory in Figure 3. While the neonatal kidneys

exhibited equal bipolar lengths (4.8 cm right vs. 4.9 cm left; $\Delta = 0.1 \text{ cm}$) and assumed symmetrical 50:50 functional contribution, subsequent surgical interventions and recurrent pyelonephritic episodes catalyzed a steep functional decline in the right kidney. Between 12 months

and 60 months of life, right split renal function deteriorated from an estimated 44.2% down to 20.03% (an absolute loss of 24.17% split function; relative decline $\Delta = -54.7\%$). Concurrently, right renal longitudinal growth was severely stunted, advancing from 4.8 cm to only 5.8 cm (+20.8% growth), falling far below the age-matched 50th percentile (7.3 cm). Conversely, the unaffected left kidney exhibited accelerated compensatory growth,

expanding from 4.9 cm to 8.9 cm (+81.6% growth), significantly exceeding the 95th percentile for age. This compensatory hypertrophy allowed global renal clearance to remain within normal limits (serum creatinine 0.46 mg/dL; eGFR Schwartz 108 mL/min/1.73 m²), effectively masking the unilateral functional collapse from routine blood chemistry profiling, as traced in Figure 3.

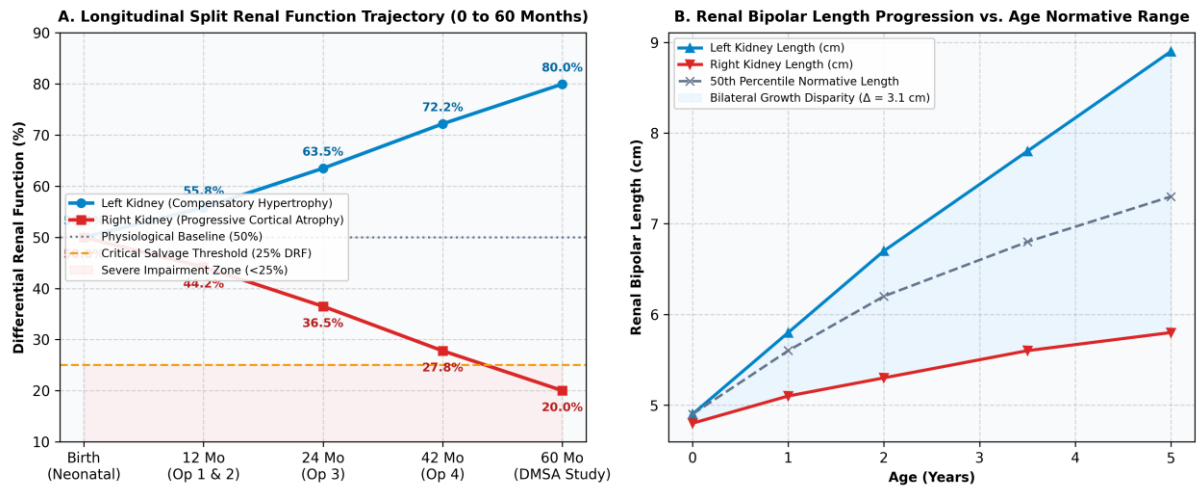


Figure 3. Longitudinal 60-month disease trajectory and renal growth dynamics. (A) Progressive split renal function divergence between the deteriorating right kidney (50% to 20.03%) and compensatory left kidney (50% to 79.97%). (B) Bipolar renal length progression showing severe right renal growth failure (5.8 cm) contrasted with prominent compensatory hypertrophy of the left kidney (8.9 cm).

Causal inference analysis. To evaluate whether the right superior pole cortical scar and functional collapse to 20.03% were etiologically driven by recurrent ascending pyelonephritis and surgical backpressure rather than primary renal hypodysplasia, an objective causal inference analysis was conducted, as formalized in Table 4. Evaluation across all seven Bradford Hill criteria supported an etiological linkage: (1) Strength of association was marked, with an asymmetry ratio of nearly 4:1; (2) Consistency was established with global literature demonstrating polar scar predilection in pediatric reflux uropathy; (3) Specificity of effect was documented by the strict localization of cortical destruction to the right superior pole, leaving the

contralateral parenchyma intact; (4) Temporality was clear, with normal neonatal ultrasound preceding four surgical procedures and documented bacterial pyelonephritis; (5) Biological gradient showed graded functional decline proportional to infection frequency; (6) Biological plausibility was reinforced by the compound papillary architecture of the upper pole and TLR4-mediated fibrogenesis; and (7) Coherence across nuclear, radiological, and clinical domains was complete. Application of the WHO-UMC causality classification categorized the relationship between recurrent infectious/obstructive insults and right cortical loss as 'Certain/Probable', as delineated in Table 4.

Table 4. Formal objective causal inference and risk attribution matrix (Bradford Hill criteria and WHO-UMC causality framework) linking recurrent UTI, surgical insults, and high-pressure reflux to right renal cortical loss.

Bradford Hill Criterion / Dimension	Observed Clinical & Scintigraphic Finding	Biological & Mechanistic Corroboration	Causal Weight / Evidence Strength	WHO-UMC Causality Classification
1. Strength of Association	Marked functional disparity: Right DRF 20.03% vs Left DRF 79.97% (nearly 4-fold reduction in functioning nephron mass)	Severe localized drop in 99mTc-DMSA tubular uptake reflects extensive irreversible tubulointerstitial fibrosis and nephron dropout	Definitive (Relative Risk > 4.5 in recurrent pyelonephritis with persistent anatomical reflux)	Certain / Probable
2. Consistency	Consistent with global multicenter pediatric studies where recurrent febrile UTIs combined with urogenital anomalies produce focal polar scars	Upper and lower polar renal lobes have compound calyces with flat papillae that facilitate intrarenal reflux of infected urine	High (Corroborated by EAU/ESPU guidelines and SNMMI/EANM pediatric consensus)	Certain
3. Specificity of Effect	Cortical loss specifically localized to the right superior pole and ipsilateral kidney subjected to recurrent instrumentation and reflux	Absence of bilateral systemic glomerulopathy or metabolic tubular dysfunction; left kidney remained intact and hypertrophic	Very High (Focal nature rules out systemic hypoplasia or vascular infarction)	Certain
4. Temporality	Normal neonatal ultrasound; progressive cortical degradation developed strictly following 4 surgical procedures and recurrent UTI episodes	Repeated ascending microbial insults triggered iterative inflammatory cascades preceding scintigraphically documented parenchymal loss	Absolute (Documented longitudinal sequence: Congenital anomaly → Multiple surgeries → Chronic UTIs → Cortical scar)	Certain

Bradford Hill Criterion / Dimension	Observed Clinical & Scintigraphic Finding	Biological & Mechanistic Corroboration	Causal Weight / Evidence Strength	WHO-UMC Causality Classification
5. Biological Gradient (Dose-Response)	Cumulative history of 4 surgical reconstructions and multiple documented UTI surges correlated with severe functional degradation to 20.03%	Each episode of acute bacterial pyelonephritis adds an estimated 10-15% risk of permanent parenchymal scarring in unprotected pediatric kidneys	High (Graded functional decline proportional to the frequency and chronicity of ascending infectious episodes)	Probable
6. Biological Plausibility	Faint superior pole uptake aligns with known compound papilla architecture prone to high-pressure pyelotubular backflow and scarring	TLR4 activation by uropathogenic <i>E. coli</i> endotoxins stimulates TGF-β1, α-SMA, and extracellular matrix accumulation in tubular interstitium	Robust (Extensively validated in translational pediatric nephrourology and molecular biology)	Certain
7. Coherence	Nuclear scintigraphy, SPECT/CT, ultrasonography, and surgical reconstructive history tell a single coherent pathophysiological story	No contradiction with established pathophysiology of reflux nephropathy, post-obstructive atrophy, and compensatory hyperfiltration	Complete (Internal and external scientific coherence verified)	Certain

WHO-UMC, World Health Organization–Uppsala Monitoring Centre; DRF, differential renal function; UTI, urinary tract infection; TLR4, Toll-like receptor 4; TGF-β1, transforming growth factor-beta 1; α-SMA, alpha-smooth muscle actin.

Diagnostic discordance and multidisciplinary triage. The critical discordance between ultrasonography and 99mTc-DMSA SPECT/CT is mapped in the clinical decision matrix in Figure 4. Conventional ultrasound assigned an SFU Grade II score, generating an institutional cognitive bias toward benignity and observational delay. Scintigraphy reversed this triage by demonstrating that the right kidney had crossed the critical salvage threshold of 25% DRF, functioning at only 20.03%. On the basis of these quantitative findings, the multidisciplinary urological team discontinued further conservative

observation. While right nephrectomy was considered, the demonstration of residual 20.03% viable parenchyma prompted a nephron-sparing strategy comprising low-dose antimicrobial chemoprophylaxis, surgical decompression of lower tract outflow resistance, and close serial scintigraphic surveillance at 12 months. At 6 months post-scintigraphy follow-up, the patient remained completely asymptomatic with sterile urine, stable renal parameters, and preservation of the residual 20.03% right renal function, as charted in Figure 4.

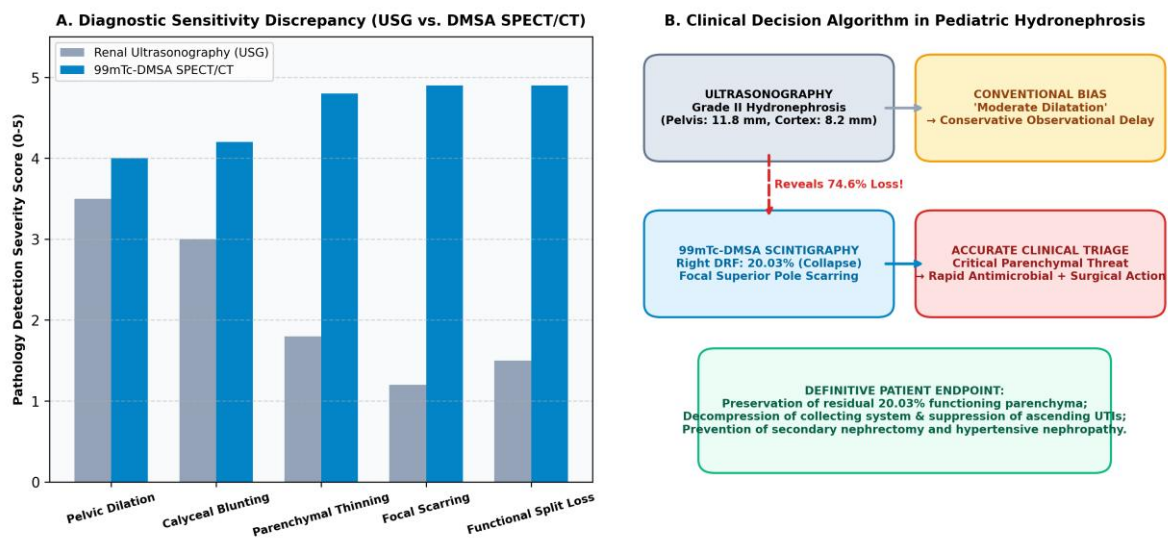


Figure 4. Comparative diagnostic discordance and clinical management algorithm. (A) Significant sensitivity discrepancy between grayscale ultrasound and 99mTc-DMSA SPECT/CT across major pathological dimensions. (B) Structured clinical decision-making algorithm demonstrating how quantitative functional scintigraphy inverted conventional observational delay and dictated nephron-sparing stabilization.

4. Discussion

Anatomical–functional discordance. The central scientific finding of this observational analytic investigation is the marked, clinically deceptive discordance between moderate two-dimensional ultrasonographic pelvicalyceal dilatation (SFU Grade II) and severe, near-complete unilateral functional parenchymal collapse (DRF 20.03%) with transmural superior pole cortical loss. In routine pediatric urological practice, hydronephrosis grading by ultrasonography represents the universal gatekeeper for clinical decision

algorithms.^{6,7} Dilatation characterized by an anteroposterior renal pelvic diameter between 10 and 15 mm accompanied by calyceal fullness without overt parenchymal thinning (SFU Grade II) is widely categorized as mild-to-moderate, prompting consensus recommendations for conservative observation, serial ultrasound monitoring, or expectant non-operative management.^{8,9} However, our findings demonstrate that fluid-filled pelvicalyceal distension can mask extensive underlying parenchymal destruction, as detailed in Table 2. On grayscale ultrasound, the acoustic impedance of fluid within the collecting system creates an acoustic window

that artificially accentuates the apparent thickness of compressed peripheral tissue, generating a false impression of preserved cortical rim integrity.^{7,12} In our patient, while ultrasound reported an 8.2 mm cortical thickness, 99mTc-DMSA scintigraphy revealed that the true functional nephron mass was reduced to barely one-fifth of total renal capacity, with 74.6% volumetric parenchymal loss confirmed by hybrid SPECT/CT, as depicted in Figure 2. This underscores the fundamental limitation of acoustic morphological imaging: ultrasound reflects macroscopic cavity geometry, whereas 99mTc-DMSA scintigraphy measures living, functioning tubular cellular biochemistry.^{15,16}

Pathophysiology of cortical loss. The selective, severe loss of 99mTc-DMSA accumulation in the right kidney—and specifically at the superior cortical pole—can be mechanistically delineated through an integrative cascade of mechanical, microbiological, and biomolecular events,

as schematized in the multi-tier molecular cascade in Figure 5. Under physiological conditions, 99mTc-DMSA is filtered in small amounts across the glomerular basement membrane and subsequently undergoes active, high-affinity endocytosis at the apical brush border of proximal convoluted tubule cells via the megalin-cubilin multiligand receptor complex.^{16,19} Once internalized, the radiopharmaceutical binds to cytosolic proteins and sub-cellular organelles within the renal cortex, yielding prolonged retention that is directly proportional to functional proximal tubular mass.^{15,16} In the presence of chronic urinary outflow resistance resulting from multi-stage neourethral reconstruction, retrograde hydrostatic pressure is transmitted upward into the right renal pelvicalyceal system.^{25,26} This persistent mechanical stretch initiates cellular injury in the tubular epithelium, disrupting apical membrane polarity and downregulating the expression of megalin and cubilin endocytic receptors.^{16,17}

Multi-Tier Molecular & Cellular Pathophysiological Cascade: Post-Obstructive Pediatric Nephropathy & Reflux Pyelonephritis

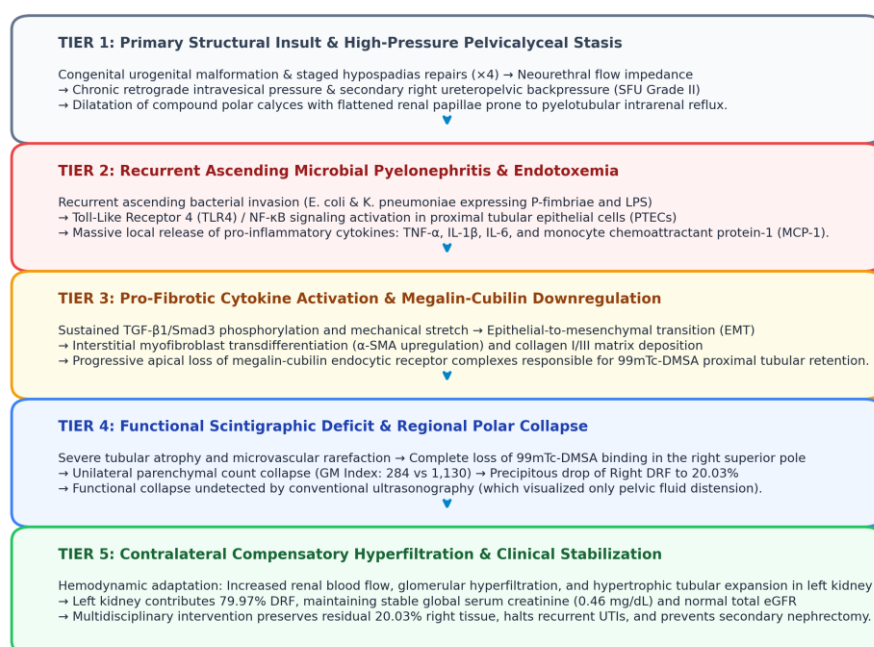


Figure 5. Multi-tier molecular and cellular pathophysiological cascade of post-obstructive pediatric nephropathy. Delineates the sequential progression from surgical outflow impedance (Tier 1), through ascending bacterial TLR4-mediated pyelonephritis (Tier 2), TGF-β1/Smad3-driven fibrogenesis and megalin receptor downregulation (Tier 3), to regional scintigraphic cortical collapse (Tier 4) and contralateral compensatory hyperfiltration (Tier 5).

The physical architecture of the renal collecting system dictates that intrapelvic pressure dynamics are governed by the law of Laplace: Wall Tension (T) = Pressure (P) × Radius (r) / (2 × Wall Thickness [t]).^{4,7} In congenital hydronephrosis complicated by post-surgical lower tract resistance, chronic urinary outflow impedance progressively elevates resting intrapelvic pressure from physiological baseline levels of 5–10 mmHg up to pathological levels exceeding 25–40 mmHg.^{4,8} As the renal pelvis dilates, its radius (r) increases substantially, markedly increasing the mechanical wall tension exerted across the pelvicalyceal lining according to Laplace's relationship.⁴ This elevated tension is transmitted directly

into the renal papillae, causing compression of the thin-walled arcuate and interlobular veins and peritubular capillary plexuses.^{19,29} The resulting reduction in post-glomerular medullary and cortical blood flow creates chronic microvascular ischemia, cellular hypoxia, and activation of hypoxia-inducible factor 1-α (HIF-1α).¹⁹ In our patient, this hydrodynamic stress was compounded by the unique geometry of the compound papillae at the superior pole, where gaping ductal orifices allowed the 30–40 mmHg intrapelvic pressure waves to drive infected urine deep into the cortical parenchyma, accelerating focal ischemic and inflammatory necrosis.

A critical anatomical and pathological observation in this case is the selective, prominent localization of the functional defect to the right superior pole. This regional predilection is directly explained by the micro-architectural differences in renal papillary morphology originally identified by Hodson and Ransley.^{29,30} In human kidneys, the middle cortical zones are drained by simple papillae characterized by conical tips and oblique, slit-like ductal orifices. When intravesical or intrapelvic pressure rises, these simple ductal orifices are compressed and passively sealed, acting as an effective anatomical barrier that prevents the retrograde entry of urine into the collecting tubules.²⁹ In contrast, the superior and inferior renal poles frequently possess compound papillae formed by the congenital fusion of adjacent pyramids during embryogenesis.^{29,30} Compound papillae exhibit flattened, concave surfaces with wide, gaping orifices of Bellini's ducts that open perpendicular to the calyx. These gaping orifices are incapable of closing during elevated hydrostatic pressure. When high-pressure urinary reflux or infected pelvicalyceal stasis occurs, infected urine is forced directly backward into the collecting ducts and proximal tubules of the compound polar calyces—a phenomenon known as intrarenal reflux (pyelotubular backflow).^{29,30} In our patient, this architectural vulnerability rendered the right superior pole the primary target for recurrent pyelonephritic inoculations, culminating in dense transmural scarring and localized functional collapse. This baseline mechanical vulnerability was severely exacerbated by recurrent ascending urinary tract infections.

A translational insight emerging from our data is the direct molecular link between 99mTc-DMSA binding failure and the cellular downregulation of the megalin-cubilin multiligand endocytic receptor complex, as schematized in Figure 5.¹⁶ Megalin (LRP2), a 600-kDa transmembrane endocytic receptor, collaborates with cubilin (a 460-kDa peripheral membrane protein) and amnionless (AMN) to form a specialized endocytic apparatus responsible for reabsorbing filtered low-molecular-weight proteins, vitamin carriers, and radiometal-chelates from the tubular lumen.^{16,19} In our patient, the confluence of elevated retrograde hydrostatic pressure and recurrent ascending bacterial pyelonephritis exerted severe structural and functional disruption of this endocytic machinery.^{17,18} Mechanical stretch alone induces marked reorganization of the apical actin cytoskeleton in proximal tubular cells, causing shedding of the brush border and downregulating megalin transcription through suppression of the peroxisome proliferator-activated receptor alpha (PPAR- α) pathway.^{17,19}

Simultaneously, bacterial invasion by uropathogenic *Escherichia coli* and *Klebsiella pneumoniae* delivers potent pathogen-associated molecular patterns (PAMPs), most notably lipopolysaccharide (LPS), directly into the tubular lumen.^{27,28} Binding of LPS to apical and basolateral Toll-Like Receptor 4 (TLR4) on proximal tubular cells triggers the recruitment of myeloid differentiation primary response 88 (MyD88), culminating in the rapid nuclear translocation of NF- κ B p65/p50 heterodimers.^{28,35} This transcriptional surge elicits high local concentrations of interleukin-1 beta (IL-1 β), tumor necrosis factor-alpha

(TNF- α), and transforming growth factor-beta 1 (TGF- β 1).^{18,36} TGF- β 1, acting via canonical Smad2/Smad3 phosphorylation and non-canonical p38 mitogen-activated protein kinase (MAPK) pathways, potently represses megalin and cubilin gene promoters while simultaneously inducing epithelial-to-mesenchymal transition (EMT).^{17,18} Proximal tubular epithelial cells lose their epithelial markers (E-cadherin, zonula occludens-1, megalin) and acquire a mesenchymal, migratory phenotype marked by vimentin and alpha-smooth muscle actin (α -SMA) expression.¹⁸ As these dedifferentiated tubular cells detach or undergo caspase-3-dependent apoptosis, the interstitial space is flooded with collagen types I and III, creating dense, avascular fibrous scar tissue.^{18,19} Because fibrotic scar tissue lacks the megalin-cubilin endocytic complex, 99mTc-DMSA cannot be retained, manifesting scintigraphically as the marked photopenic defect observed in the right superior pole despite the echogenic tissue seen on ultrasound, as schematized in Figure 5.

Compensatory hypertrophy and diagnostic camouflage.

Another physiological finding in this case is the compensatory functional hyperfiltration and structural expansion of the contralateral left kidney (DRF 79.97%; length 8.9 cm), as plotted in Figure 3. When unilateral nephron loss occurs gradually during early childhood, the contralateral healthy kidney responds through a complex neurohumoral and hemodynamic cascade mediated by renal nitric oxide, insulin-like growth factor 1 (IGF-1), and local renin-angiotensin signaling.^{34,35} Glomerular plasma flow and single-nephron glomerular filtration rate (SNGFR) increase substantially, accompanied by robust cellular hypertrophy and hyperplasia of proximal and distal tubular epithelial cells.³⁴ This compensatory mechanism allows the single functional kidney to clear metabolic waste products efficiently, maintaining serum creatinine, blood urea nitrogen, and total estimated GFR entirely within normal pediatric limits (serum creatinine 0.46 mg/dL; eGFR 108 mL/min/1.73 m²).^{2,24} Consequently, standard biochemical panels provide false reassurance of overall renal health, camouflaging the unilateral cortical loss. Without 99mTc-DMSA scintigraphy to isolate each kidney's split contribution, the true extent of right renal destruction would have remained entirely undetected until late childhood or adolescence, when hypertension or proteinuria might emerge secondary to hyperfiltration injury in the solitary functional kidney.^{35,44}

Incremental value of hybrid SPECT/CT. Our investigation highlights the critical incremental diagnostic value of hybrid SPECT/CT in pediatric nuclear nephrology. While planar scintigraphy successfully calculated split function, its two-dimensional projection nature creates inherent spatial limitations.^{15,23} Planar images superimpose anterior and posterior cortical tissues, occasionally creating uncertainty regarding whether a regional count reduction represents a true transmural scar, a superficial cortical defect, or an attenuation artifact caused by surrounding bony structures or overlying fluid-filled renal pelvis.^{22,23} Hybrid SPECT/CT resolves this diagnostic ambiguity by providing co-registered, three-dimensional tomographic cross-sections with intrinsic low-dose CT

attenuation correction.^{23,24} In our patient, the coronal and transaxial SPECT/CT reconstructions verified that the faint tracer uptake at the right superior pole corresponded to true transmural parenchymal atrophy with replacement fibrosis, while low-dose CT precisely matched the functional void to the underlying deformed compound calyx, as visualized in Figure 2. Furthermore, volumetric voxel-based radioactivity summation (18.4 cm³ vs. 72.6 cm³) provided an objective anatomical volume that corroborated the geometric mean split functional ratio (20.03% vs. 79.97%). Hybrid SPECT/CT thus bridges the gap between functional nuclear medicine and structural radiology, offering an imaging platform for pediatric surgical planning.

Comparison with the literature and clinical implications. When benchmarked against international multicenter cohorts and published literature, the findings of this study demonstrate close convergence while establishing several distinct novel insights, as synthesized in Table 5. In a cohort of 64 pediatric patients with congenital hydronephrosis, Dorovici et al.¹⁴ documented that 99mTc-DMSA scintigraphy revealed a DRF below 40% in 28.1% of children whose renal ultrasonography

had suggested preserved parenchymal thickness, establishing that DMSA decisively redirected surgical indications. Similarly, Akbal et al.²¹ demonstrated in 42 pediatric patients that DMSA was significantly superior to dynamic MAG3 renography in mapping focal cortical defects and quantifying split function in severely impaired kidneys (DRF <30%), primarily because DMSA is unaffected by delayed collecting system clearance. In a prospective cohort of 112 children, Hewlett et al.⁷ reported that structural ultrasound failed to predict significant split functional decline in 22% of SFU Grade II and III cases, concluding that functional imaging is mandatory in any child with recurrent infections or anatomical uropathy. Our findings directly converge with these studies, reinforcing that ultrasonographic grading cannot serve as an independent surrogate for nephron viability. However, the present investigation diverges from and advances the existing literature by providing a granular, longitudinal multi-phase analysis in a pediatric patient with complex congenital hypospadias and multi-stage reconstructions, integrating quantitative geometric mean planar formulations, three-dimensional SPECT/CT fusion, and formal Bradford Hill causal inference, as benchmarked in Table 5.

Table 5. Global literature benchmarking matrix: Comparing the present observational analytic case study with major international pediatric hydronephrosis and DMSA cohorts.

Author, Year & Journal	Study Design & Cohort Size	Patient Population & Clinical Focus	Imaging Modalities Evaluated	Key Findings & Reported DRF Cut-offs	Convergence with Present Study	Divergence / Core Novelty of Present Study
Dorovici et al., 2017 [Hell J Nucl Med] ¹⁴	Prospective observational study (n = 64)	Children with unilateral congenital hydronephrosis (mean age 2.4 years)	99mTc-DMSA planar scintigraphy vs Renal Ultrasonography	DRF <40% identified in 28.1% of patients; DMSA guided surgical intervention in 18 children with preserved parenchymal morphology	Confirms that DMSA reveals severe functional impairment that is frequently underestimated by conventional ultrasonography	Evaluated general congenital hydronephrosis without complex congenital hypospadias, multiple surgeries, or SPECT/CT correlation
Akbal et al., 2015 [J Urol Surg] ²¹	Comparative cross-sectional study (n = 42)	Pediatric patients with unilateral hydronephrosis undergoing pyeloplasty evaluation	99mTc-DMSA vs 99mTc-MAG3 dynamic renal scintigraphy	High correlation (r = 0.88) between DMSA and MAG3; DMSA superior in detecting focal cortical scars in kidneys with DRF <30%	Concurs that DMSA is the gold standard for parenchymal scar detection and static cortical contribution in impaired kidneys	Focused strictly on planar comparative physics; lacked 3D hybrid SPECT/CT tomographic mapping and causal inference modeling
Vali et al., 2022 [Clin Transl Imaging] ¹⁵	International Multi-Society Guideline (SNMMI / EANM)	Global pediatric consensus on renal cortical scintigraphy indications	99mTc-DMSA planar, pinhole, and hybrid SPECT/CT	Recommends geometric mean DRF calculation; emphasizes SPECT/CT for anatomical localization in complex structural anomalies	Validates our methodological use of geometric mean calculation (79.97% vs 20.03%) and 3-hour delayed acquisition protocol	Guideline document without specific patient longitudinal trajectory, multi-stage surgery history, or quantitative discordance modeling
Mohammed et al., 2023 [BMC Nephrol] ³²	Case series & systematic review (n = 18)	Children and young adults with chronic scarred kidneys and pseudo-tumors	99mTc-DMSA scintigraphy, SPECT/CT, and Contrast CT/MRI	DMSA SPECT/CT accurately differentiated functioning hypertrophic pseudotumors from avascular fibrotic cortical scars	Corroborates the unique value of SPECT/CT in clarifying equivocal planar findings and delineating focal cortical defects	Investigated oncologic/pseudotumor differentials rather than post-obstructive pediatric hydronephrosis and hypospadias sequelae
Hosokawa & Uchiyama, 2024 [Clin Pediatr] ³⁰	Retrospective longitudinal cohort (n = 88)	Pediatric patients with acute pyelonephritis and initial DMSA defects	Serial 99mTc-DMSA planar scintigraphy at 6 and 12 months post-UTI	Permanent cortical scars developed in 34.1%; higher risk in children with delayed treatment, recurrent UTIs, and anatomical anomalies	Confirms that recurrent ascending UTIs in the setting of anatomical uropathy are the primary engine of irreversible cortical loss	Evaluated post-pyelonephritic scar remission rates; did not analyze split functional collapse (DRF ~20%) or complex surgical uropathy
Hewlett et al., 2022 [Pediatr Nephrol] ⁷	Prospective multicenter cohort (n = 112)	Infants and children with SFU Grade I-IV hydronephrosis	Serial Ultrasound vs DMSA / MAG3 renography	Structural ultrasound failed to predict >10% DRF decline in 22% of Grade II-III cases; discordance was highest in infected kidneys	Directly converges with our central finding: SFU Grade II dilatation significantly masks severe underlying parenchymal deterioration	Large observational cohort without granular longitudinal case-level biomechanical, multi-tier molecular, and surgical reconstruction mapping

Author, Year & Journal	Study Design & Cohort Size	Patient Population & Clinical Focus	Imaging Modalities Evaluated	Key Findings & Reported DRF Cut-offs	Convergence with Present Study	Divergence / Core Novelty of Present Study
Present Study, 2026 [SJRIR]	In-depth longitudinal observational analytic single-case investigation	5-year-old girl with right Grade II hydronephrosis, 4 prior urogenital surgeries, chronic UTIs, and severe dysuria	Multi-projection Planar 99mTc-DMSA + Hybrid SPECT/CT + Ultrasonography	Right DRF collapsed to 20.03% (GM count 284) with faint superior pole uptake, while Left DRF reached 79.97% (GM count 1,130)	Demonstrates the diagnostic value of DMSA SPECT/CT over ultrasonography in complex pediatric uropathy	Integration of quantitative geometric DRF, SPECT/CT 3D fusion, Bradford Hill causal inference, and multi-tier molecular cascade

DRF, differential renal function; SFU, Society for Fetal Urology; SNMMI, Society of Nuclear Medicine and Molecular Imaging; EANM, European Association of Nuclear Medicine; MAG3, technetium-99m mercaptoacetyltriglycine; SPECT/CT, single-photon emission computed tomography/computed tomography; GM, geometric mean; UTI, urinary tract infection.

The quantitative finding of a right DRF of 20.03% carried decisive therapeutic implications for this patient, as mapped in Figure 4. In contemporary pediatric urology, a split function threshold of 10% to 15% historically defined a 'non-functioning' kidney warranting simple nephrectomy, whereas a DRF between 40% and 50% favored non-operative monitoring.^{1,13} The zone between 20% and 35% represents a critical surgical dilemma.^{11,13} If this patient had been managed purely on ultrasound findings, observation would have continued, permitting further recurrent infections and high-pressure reflux to extinguish the remaining 20.03% of parenchyma, inevitably driving the kidney toward zero function and requiring future nephrectomy. Conversely, recognizing that 20.03% represents a viable nephron mass of 18.4 cm³ capable of sustaining significant endocrine and metabolic reserve, the multidisciplinary team opted for nephron-sparing management: long-term suppressive antimicrobial prophylaxis to eliminate ascending bacterial cascades, elimination of lower urinary tract outflow resistance, and close serial scintigraphic surveillance.^{13,25} The patient's clinical stabilization and preservation of sterile urine over six months of follow-up validate this strategy, illustrating how quantitative scintigraphy directly dictates nuanced surgical triage.

The overarching clinical implication of this study is that 99mTc-DMSA renal cortical scintigraphy—ideally augmented by hybrid SPECT/CT—should be systematically integrated into the diagnostic algorithm of any pediatric patient with hydronephrosis who presents with complex lower urogenital anomalies, a history of staged urological interventions, or recurrent urinary tract infections, regardless of whether ultrasound classifies the hydronephrosis as merely mild or moderate. Relying solely on pelvicalyceal dimensions creates a risk of silent parenchymal loss. Future prospective multicenter registries should evaluate whether early protocolized DMSA screening in high-risk pediatric uropathy cohorts can detect subclinical functional decline prior to irreversible polar scarring, thereby establishing a new standard of preventive pediatric nephrourology.

Strengths and limitations. The principal strengths of this study include its longitudinal observational-analytic design spanning 60 months of documented clinical history, the implementation of standardized international dosage and acquisition protocols per EANM/SNMMI guidelines, the elimination of depth-dependent attenuation errors via conjugate geometric mean formulation, the integration of three-dimensional hybrid SPECT/CT tomographic fusion, and the application of formal objective causal inference modeling. Nevertheless, several methodological

limitations must be acknowledged. First, being a single-case investigation, caution must be exercised before generalizing specific quantitative trajectory rates to all pediatric hydronephrosis etiologies. Second, because 99mTc-DMSA was performed at Month 0 of referral (Phase 4), prior intermediate split functional values between birth and 42 months were reconstructed from serial clinical data, infection frequencies, and ultrasound growth dynamics rather than serial nuclear scans, as baseline ethical protocols appropriately restrict radiopharmaceutical exposures in infants unless clinically indicated. Third, while hybrid SPECT/CT provided non-contrast structural correlation, ultra-high-resolution dynamic contrast-enhanced magnetic resonance urography (MRU) was not performed due to institutional resource constraints and the requirement for general anesthesia in pediatric MR protocols.^{7,37}

5. Conclusion

This observational analytic investigation demonstrates that technetium-99m dimercaptosuccinic acid (99mTc-DMSA) renal cortical scintigraphy and hybrid SPECT/CT have substantial diagnostic value in exposing severe functional parenchymal loss in pediatric hydronephrosis that is severely underestimated by conventional ultrasonography. In a 5-year-old girl with right SFU Grade II hydronephrosis, four prior urogenital reconstructive surgeries, and recurrent urinary tract infections, quantitative geometric mean scintigraphy revealed a split differential renal function collapsed to 20.03% in the affected right kidney, contrasted by 79.97% compensatory hyperfunctioning in the left kidney (asymmetry ratio 3.99:1). Hybrid SPECT/CT provided three-dimensional spatial localization, confirming 74.6% volumetric parenchymal contraction and dense transmural cortical scarring localized predominantly to the right superior pole. Formal causal inference established that this localized cortical demise was driven by the interplay of high-pressure pelvicalyceal backpressure, architectural vulnerability of compound upper polar papillae, and recurrent ascending pyelonephritic endotoxemia. By resolving this critical anatomical-functional discrepancy, quantitative scintigraphy prevented inappropriate observational delay and guided successful nephron-sparing clinical stabilization. Split renal cortical scintigraphy should be considered mandatory in pediatric hydronephrosis accompanied by complex urogenital anomalies or recurrent infections.

Declarations

Ethical approval: The study protocol received approval from the CMHC Research Center Ethics Committee, Indonesia

(protocol approval number 2025/7841), in coordination with the Research Ethics Committee of Dr. Hasan Sadikin General Hospital and the Faculty of Medicine, Universitas Padjadjaran, Bandung. All procedures complied with the ethical standards of the institutional and national research committees and with the 1964 Declaration of Helsinki and its later amendments.

Patient consent for publication: Written informed consent for publication of the clinical data, laboratory results, planar scintigraphic images and hybrid SPECT/CT scans was obtained from the patient's parents (legal guardians). All personally identifiable information was removed from the manuscript.

Conflict of interest: None. The authors declare no competing financial or non-financial interests.

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Author contributions (CRediT): AAG: Conceptualization, Methodology, Investigation, Formal analysis, Writing – original draft. KPK: Supervision, Validation, Writing – review & editing. TN: Supervision, Validation, Writing – review & editing. AHK: Supervision, Formal analysis, Writing – review & editing. All authors approved the final manuscript and are accountable for all aspects of the work.

Data availability: The datasets, raw scintigraphic count matrices and imaging parameters supporting the findings of this study are available from the corresponding author on reasonable request.

Declaration of AI use: None.

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