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Predictive Value of Systemic and Urinary Biomarkers for Kidney Scarring after a first febrile urinary tract infection in children: a prospective cohort study

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Predictive Value of Systemic and Urinary Biomarkers for Kidney Scarring after a first febrile urinary tract infection in children: a prospective cohort study

Short title: Biomarkers and kidney scarring after first febrile UTI

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Abstract

Background: Delayed dimercaptosuccinic acid (DMSA) scintigraphy is increasingly selective after febrile urinary tract infection (fUTI), creating a need for reliable non-invasive risk markers. We evaluated systemic and urinary biomarkers, microbiological profiles, and ultrasound findings to predict DMSA-defined kidney scarring following a first fUTI.

Methods: This prospective cohort included 83 children with first fUTI or any fUTI with previous normal DMSA scintigraphy. Pre-antibiotic urine sample was analyzed for urinary kidney injury molecule-1 (uKIM-1), neutrophil gelatinase-associated lipocalin (uNGAL), pentraxin-3 (uPTX3), and creatinine (uCr). Delayed DMSA scintigraphy and voiding cystourethrography (VCUG) were clinically indicated rather than universal. Analyses included ROC curves, bootstrap confidence intervals, paired DeLong comparison, exploratory cutoffs, and sensitivity analyses.

Results: Dimercaptosuccinic acid scintigraphy was available in 45 children; 16 had kidney scars. Procalcitonin discriminated scarring better than CRP in the common analytic population (AUC 0.626 vs 0.429; DeLong p=0.028). Urinary pentraxin-3/uCr had the highest apparent urinary AUC (0.727), but the signal did not survive false-discovery-rate correction and was attenuated after excluding zero-coded uPTX3 values. Non-E. coli infection was strongly associated with scarring (OR 9.43, 95% CI 2.29-38.84). Among 54 children underwent VCUG, 19 were diagnosed with VUR and 17 high-grade VUR; abnormal ultrasound was associated with any VUR (OR 4.29) and high-grade VUR (OR 4.33). Exploratory biomarker cutoffs showed no marker with both high sensitivity and high specificity for scarring.

Conclusions: Procalcitonin outperformed CRP in scar detection, but demonstrated only moderate standalone discrimination. Neither urinary biomarkers nor internally derived cutoffs proved robust enough for independent clinical use. Risk stratification should integrate microbiology, systemic inflammation, and imaging, and requires external validation.

Keywords: febrile urinary tract infection; kidney scarring; procalcitonin; kidney injury molecule-1; neutrophil gelatinase-associated lipocalin; pentraxin-3

Introduction

Febrile urinary tract infection (fUTI) is among the most important bacterial infections of infancy and childhood. A subset of children may have acute kidney parenchymal involvement, vesicoureteral reflux (VUR), recurrent infection, or permanent kidney scarring [1-7]. The reported frequency of scarring after a first UTI varies substantially across cohorts because of differences in age, case mix, VUR prevalence, timing of treatment, and imaging protocols [4,6], while studies of treatment timing have reported differing associations with later scarring [8,9].

Delayed technetium-99m dimercaptosuccinic acid (DMSA) scintigraphy remains the reference imaging method for cortical scarring, but contemporary guidelines favor selective rather than universal nuclear imaging because of radiation exposure, resource use, and limited impact on immediate management in low-risk children [2-4]. The 2026 American Academy of Pediatrics (AAP) guideline recommends renal and bladder ultrasonography (RBUS) after a first febrile UTI in children younger than 5 years, while discouraging routine VCUG after a first fUTI when RBUS is normal, with specific exceptions that include non-E. coli infection and atypical or complicated presentations [10,11]. This makes clinically useful early risk stratification particularly relevant.

Procalcitonin (PCT) has been associated with acute pyelonephritis, high-grade VUR, and later kidney scarring in pediatric fUTI, whereas C-reactive protein (CRP) and leukocyte count are less specific measures of systemic inflammation [12-15]. Urinary biomarkers could add complementary biological information. Urinary neutrophil gelatinase-associated lipocalin (uNGAL) reflects tubular stress and innate immune activation, urinary kidney injury molecule-1 (uKIM-1) reflects proximal tubular injury, and urinary pentraxin-3 (uPTX3) is a local inflammatory

mediator; however, assay methods, urine dilution, timing of sampling, and outcome verification vary widely across studies [15-17].

A recent systematic review and meta-analysis found higher PCT and uNGAL concentrations in children who subsequently developed kidney scarring, with moderate pooled discrimination for uNGAL, but evidence for KIM-1 and PTX3 was sparse [15]. The present prospective cohort therefore evaluated systemic inflammatory markers, uKIM-1, uNGAL, uPTX3, and urinary creatinine (uCr)-normalized ratios in relation to delayed DMSA-defined kidney scarring after a first fUTI. Secondary objectives were to examine relevant microbiological and ultrasound risk signals and to quantify the impact of selective DMSA verification.

The biological rationale for a multimarker strategy is supported by earlier and contemporary studies. Individual-patient meta-analysis has shown PCT to outperform CRP and leukocyte count for both acute pyelonephritis and late scarring [18], whereas uKIM-1, uNGAL, and uPTX3 studies have produced heterogeneous findings depending on whether the target is acute parenchymal involvement, established scars, or future scarring [19-21]. Recent systematic reviews of urinary biomarkers in children with VUR likewise report only moderate accuracy and substantial between-study heterogeneity [17,22].

Methods

Study design, setting, and participants

This was a prospective multi-center cohort study conducted at the 1st, 3rd and 4th Departments of Pediatrics, Aristotle University of Thessaloniki, Greece and Saint Luke's Hospital, Thessaloniki, Greece. Children presenting with a first microbiologically confirmed fUTI were prospectively enrolled according to the approved doctoral protocol. The present manuscript reports the prognostic biomarker component of the cohort and follows STROBE

(**Supplementary Table 1**), together with relevant STARD/TRIPOD reporting principles for discrimination analyses [23-26].

The study was approved by the Assembly/Ethics authority of the School of Medicine, Aristotle University of Thessaloniki (approval 30 May 2023; registration no. 5057; study no. 108/2023). Written informed consent was obtained from parents or legal guardians in accordance with the approved protocol.

Clinical definitions and imaging

The index fUTI was defined by fever plus a positive urine culture interpreted in conjunction with the collection method, urinalysis, symptoms, and clinical context. Clinical variables recorded at presentation included fever duration, maximum temperature, symptoms, routine laboratory measurements, and urine culture organism. Uropathogens were categorized as E. coli or non-E. coli for risk analyses. Terminology follows contemporary KDIGO recommendations, using “kidney” rather than “renal” where appropriate [27].

Kidney and bladder ultrasonography was classified as normal or abnormal based on structural or parenchymal findings documented during clinical care. VCUG was performed according to clinical indications (abnormal ultrasonography, infants under 2 months of age, atypical fUTI). Atypical fUTI was characterized by a severe clinical state, reduced urine flow, a palpable abdominal or bladder mass, elevated creatinine, bacteremia, failure to respond to appropriate antibiotic therapy within 48 hours, or infection caused by a non-E. coli microorganism. For the primary any-VUR analysis, mild and high-grade VUR were compared with normal VCUG plus other non-reflux abnormalities (19 VUR vs 35 controls; n=54); a sensitivity analysis excluded the three children with other non-reflux VCUG findings (19 vs 32; n=51). High-grade VUR was defined as grade III or higher; after the prespecified severity recoding, 17 children had high-grade VUR and 37 formed the non-high-grade reference group in the inclusive analysis.

Delayed DMSA scintigraphy was performed when clinically indicated (abnormal findings on ultrasound or VCUG, very high inflammatory markers, or an episode atypical fUTI), and served as the reference standard for the primary outcome, kidney scarring. Scars were graded using the modified Smellie/Goldraich approach; seven children had Grade 1 and nine had Grade 2 scars, and no Grade 3-4 lesions were recorded [28]. Because DMSA was not universal, the proportion with scarring among DMSA-tested children was treated as a verified-subgroup proportion rather than as a cohort incidence estimate.

Biomarker measurements

Serum CRP, PCT, white blood cell count, urea, creatinine, electrolytes, and other routine measurements were obtained at presentation. Urine samples for uKIM-1, uNGAL, uPTX3, and uCr were collected before initiation of antibiotic treatment whenever feasible.

Urinary KIM-1, uNGAL, and uPTX3 were measured using Picokine enzyme-linked immunosorbent assay kits (HUMAN KIM-1/TIM-1 ELISA KIT PICOKINE; NGAL ELISA KIT PICOKINE; HUMAN PTX3 MICROSAMPLE ELISA KIT). Urinary biomarkers were analyzed as absolute concentrations and as ratios to uCr. Three samples without valid urinary biomarker results were excluded only from urinary biomarker analyses; these children remained eligible for non-biomarker analyses. Urinary creatinine availability further reduced the sample size of normalized-ratio analyses.

Statistical analysis

Continuous variables were summarized as medians with interquartile ranges (IQR) and categorical variables as counts and percentages. Between-group comparisons used two-sided Mann-Whitney U tests for continuous variables and Fisher exact tests for categorical variables. Rank-biserial correlations and odds ratios (OR) with 95% confidence intervals (CI) were used as effect-size measures where appropriate.

Discrimination for DMSA-defined kidney scarring was evaluated using receiver operating characteristic (ROC) curves and area under the curve (AUC). For the dedicated biomarker-threshold analysis, AUC confidence intervals were estimated with 5,000 stratified bootstrap replicates in R version 4.3.3 using pROC version 1.18.5. Procalcitonin and CRP were compared directly in the same children using the paired, two-sided DeLong test [29]. Exploratory cutoffs were selected by the Youden index [30]; because they were derived and tested internally, they were not interpreted as validated clinical thresholds.

For the six urinary markers (three absolute concentrations and three uCr-normalized ratios), the Benjamini-Hochberg method controlled the false discovery rate (FDR) [31]. The primary analysis retained zero-coded uPTX3 measurements as recorded in the analytic dataset, and sensitivity analyses repeated uPTX3 analyses after excluding zero-coded values because these could represent measurements at or below assay detection limits.

Firth penalized logistic regression was used only for exploratory sensitivity modeling because the number of scar events was small [32]. Models were deliberately parsimonious and were not presented as validated prediction tools, consistent with recommendations to limit overfitting and to emphasize internal validation in small prediction datasets [33,34]. The mechanism of outcome verification was examined by comparing children who did and did not undergo delayed DMSA scan. Missing observations were handled by available-case analysis, and the denominator is reported for each analysis.

Results

Cohort characteristics and outcome verification

The cohort included 83 children with a first fUTI (**Supplementary Figure 1**); median age was 4 months (IQR 2-8), and 72 children (86.7%) were younger than 12 months (**Table 1**).

Procalcitonin was available in 77 children. Valid uKIM-1, uNGAL, and uPTX3 measurements were available in 80 children after exclusion of three invalid urinary biomarker samples.

Delayed DMSA scintigraphy was available in 45/83 children (54.2%): 16 had kidney scars and 29 had normal DMSA findings. Among the 16 scar-positive children, 7 had Grade 1 and 9 had Grade 2 lesions. Accordingly, the observed 16/45 (35.6%) scar proportion describes only the DMSA-verified subgroup and must not be interpreted as the incidence of scarring in the full cohort.

Non-E. coli organisms were substantially more frequent among children with scars than among those with normal DMSA scintigraphy (75.0% vs 24.1%; p=0.002). Fever duration and WBC count were paradoxically lower in the scar group within the DMSA-verified subset, a pattern considered in light of the non-random DMSA work-up mechanism described below.

Variable	Overall cohort	Kidney scar	Normal DMSA scintigraphy	p
Age, months	4 (2-8)	4 (1.75-8.5)	5 (3-8)	0.591
Male sex	47/83 (56.6%)	9/16 (56.2%)	16/29 (55.2%)	1.000
Prematurity	12/83 (14.5%)	1/16 (6.2%)	5/29 (17.2%)	0.399
Fever duration, days	1 (1-3)	1 (1-2)	2 (1-4)	***0.028***
Maximum temperature, °C	38.4 (37.75-39)	38.25 (37.88-38.7)	38.8 (38.4-39)	0.053
CRP, mg/dL	2.71 (0.56-9.05)	6.38 (1.44-14.69)	6.21 (2.71-17.26)	0.577
PCT, ng/mL	0.22 (0.07-1.40)	3.35 (0.24-7.54)	0.46 (0.28-1.96)	0.196

WBC, /µL	15,000 (10,500-19,800)	14,400 (10,258-17,400)	20,300 (15,200-25,800)	***0.015***
Urea	16 (13-23)	22 (16.75-25.25)	16 (14-23)	0.059
Creatinine	0.35 (0.32-0.41)	0.39 (0.34-0.51)	0.37 (0.33-0.44)	0.687
Non-E. coli uropathogen	34/83 (41.0%)	12/16 (75.0%)	7/29 (24.1%)	***0.002***
Abnormal ultrasound	26/83 (31.3%)	10/16 (62.5%)	11/29 (37.9%)	0.133

Table 1. Baseline characteristics of the cohort and DMSA-defined groups; *Data are median (IQR) or n/N (%); P-values compare the kidney-scar and normal-DMSA groups using Mann-Whitney U or Fisher exact tests; Procalcitonin denominators are smaller because PCT was not available in all participants; DMSA, dimercaptosuccinic acid; CRP, C-reactive protein; PCT, procalcitonin; WBC, white blood cell count.*

Biomarker distributions and discrimination for kidney scarring

Procalcitonin was numerically higher in children with kidney scars, whereas CRP distributions overlapped substantially (**Table 2; Figure 1**). In the 41 children with PCT and DMSA data, PCT had an AUC of 0.626. When PCT and CRP were compared in the same analytic population, PCT had significantly better discrimination than CRP (AUC 0.626 vs 0.429; ΔAUC 0.197; paired DeLong p=0.028) (**Figure 2**). The absolute discriminatory performance of PCT nevertheless remained only moderate.

None of the absolute urinary biomarkers showed robust separation between scar and normal-DMSA groups. Urinary KIM-1 had AUC 0.606, uNGAL AUC 0.406, and uPTX3 AUC 0.610. Among normalized markers, uPTX3/uCr had the highest apparent AUC (0.727; 95% bootstrap CI 0.537-0.884) and a nominal p-value of 0.039, but this association did not survive FDR correction (q=0.233).

The PTX3 finding was highly sensitive to assay-limit handling. Zero-coded uPTX3 values occurred in 21/80 urinary biomarker measurements overall; none occurred among the 16 scar-positive children with absolute uPTX3 data, compared with 8/28 children with normal DMSA scintigraphy. After excluding zero-coded values, the AUC of uPTX3/uCr fell to approximately 0.553, indicating that the apparent normalized PTX3 signal was not sufficiently robust for clinical interpretation.

Biomarker	Scar / normal	Kidney scar, median (IQR)	Normal DMSA, median (IQR)	p	BH-FDR q	AUC
CRP	16 / 29	6.385 (1.445-14.688)	6.210 (2.710-17.260)	0.577	—	0.448
PCT	14 / 27	3.355 (0.245-7.542)	0.460 (0.280-1.960)	0.196	—	0.626
uKIM-1	16 / 28	0.397 (0.181-1.029)	0.306 (0.116-0.444)	0.251	0.341	0.606
uNGAL	16 / 28	1.590 (1.267-1.845)	1.685 (1.248-2.494)	0.311	0.341	0.406
uPTX3	16 / 28	6.066 (3.660-13.916)	4.199 (0-13.906)	0.230	0.341	0.610
uKIM-1/uCr	12 / 18	0.051 (0.017-0.074)	0.031 (0.011-0.039)	0.341	0.341	0.606
uNGAL/uCr	12 / 18	0.127 (0.031-0.263)	0.137 (0.078-0.302)	0.182	0.341	0.352
uPTX3/uCr	12 / 18	0.488 (0.281-1.486)	0.138 (0-0.542)	***0.039***	0.233	0.727

Table 2. Biomarker distributions and discrimination for DMSA-defined kidney scarring; *Benjamini-Hochberg false discovery rate correction was applied to the family of six urinary biomarker comparisons; C-reactive protein and PCT were not part of that correction family; The uPTX3/uCr AUC was 0.727 (95% CI 0.537-0.884 by 5,000 stratified bootstrap replicates); In the matched PCT-versus-CRP population, AUCs were 0.626 and 0.429, respectively (paired DeLong p=0.028); AUC, area under the receiver operating characteristic curve; BH-FDR, Benjamini-Hochberg false discovery rate; CRP, C-reactive protein; DMSA, dimercaptosuccinic*

acid; IQR, interquartile range; PCT, procalcitonin; uKIM-1, urinary kidney injury molecule-1; uNGAL, urinary neutrophil gelatinase-associated lipocalin; uPTX3, urinary pentraxin-3; uCr, urinary creatinine.

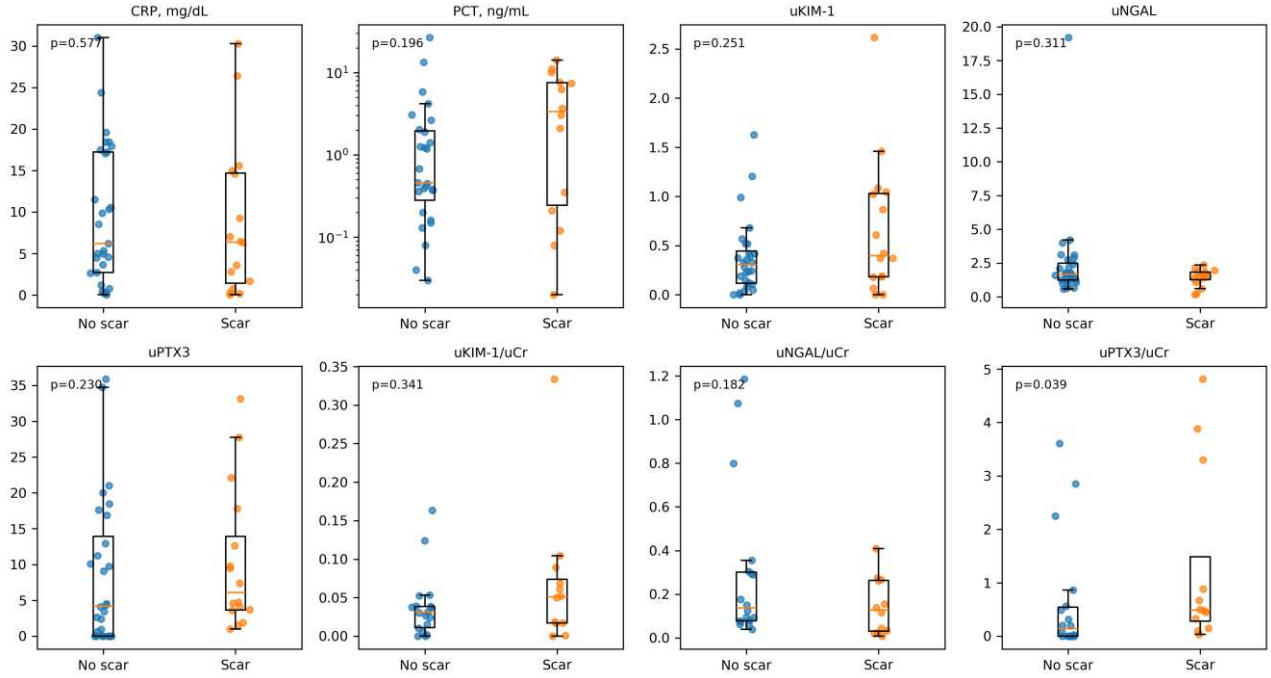


***Figure 1. Biomarker distributions according to delayed DMSA outcome**; Box-and-jitter plots compare CRP, PCT, uKIM-1, uNGAL, uPTX3, and urinary creatinine-normalized ratios between children with normal delayed DMSA scintigraphy and children with kidney scars; Displayed p-values are unadjusted Mann-Whitney U tests; The nominal uPTX3/uCr signal did not survive FDR correction and was attenuated after exclusion of zero-coded uPTX3 measurements; CRP, C-reactive protein; DMSA, dimercaptosuccinic acid; PCT, procalcitonin; uKIM-1, urinary kidney injury molecule-1; uNGAL, urinary neutrophil gelatinase-associated lipocalin; uPTX3, urinary pentraxin-3; uCr, urinary creatinine.*

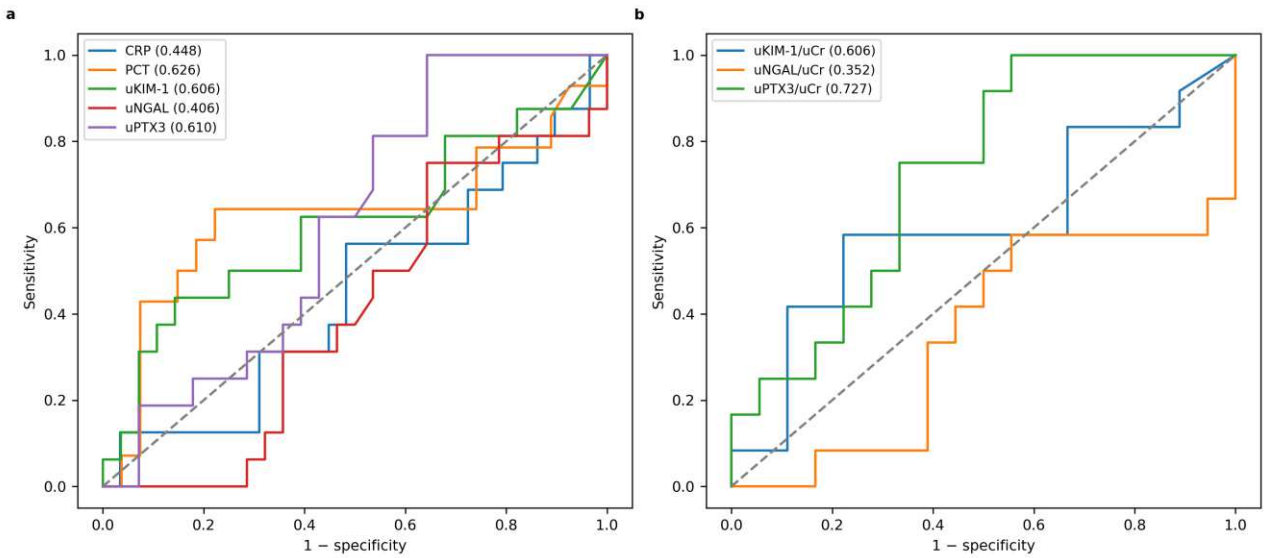


Figure 2. Receiver operating characteristic curves for biomarker discrimination of kidney scarring. *Panel a shows CRP, PCT, and absolute urinary biomarkers; Panel b shows uCr-normalized biomarkers; The plotted CRP curve uses all available CRP-DMSA pairs, whereas the formal PCT-versus-CRP comparison used the matched analytic population (PCT AUC 0.626 vs CRP AUC 0.429; paired DeLong p=0.028); CRP, C-reactive protein; DMSA, dimercaptosuccinic acid; PCT, procalcitonin; uKIM-1, urinary kidney injury molecule-1; uNGAL, urinary neutrophil gelatinase-associated lipocalin; uPTX3, urinary pentraxin-3; uCr, urinary creatinine.*

Microbiological and imaging associations

Non-E. coli infection was the strongest clinical association with DMSA-defined scarring: 12/16 (75.0%) children with scars had a non-E. coli uropathogen compared with 7/29 (24.1%) children with normal DMSA scintigraphy (OR 9.43, 95% CI 2.29-38.84; p=0.0015) (**Table 3**). Almost 2/3 of children who did not underwent DMSA scintigraphy had an E. coli infection (65.8%). Eight children had a Klebsiella fUTI, three of them had an Enterococcus fUTI and three children had a Pseudomonas, a Citrobacter and a Morganella uropathogen accordingly. This signal

remained the dominant covariate in parsimonious exploratory penalized models, although the small number of events precluded definitive multivariable model development.

Abnormal ultrasound was not significantly associated with scarring in the DMSA subset (OR 2.73, 95% CI 0.77-9.61), but it was associated with VUR. In the inclusive VCUG analysis (n=54), abnormal ultrasound had 63.2% sensitivity and 71.4% specificity for any VUR (OR 4.29, 95% CI 1.31-14.03; p=0.020) and 64.7% sensitivity and 70.3% specificity for high-grade VUR (OR 4.33, 95% CI 1.28-14.67; p=0.020). Excluding three non-reflux “other” VCUG findings produced similar estimates for any VUR (OR 4.38, 95% CI 1.31-14.68). CRP, uKIM-1, and uPTX3 showed nominal differences in some VUR comparisons, but none remained significant after FDR correction (**Table 5**).

Association	Analytic n	OR	95% CI	p
Non-E. coli uropathogen → kidney scar	45	9.43	2.29-38.84	***0.0015***
Abnormal ultrasound → kidney scar	45	2.73	0.77-9.61	0.133

Table 3. Key clinical associations with DMSA-defined kidney scarring; *CI, confidence interval; DMSA scintigraphy was performed selectively. OR, odds ratio; DMSA, dimercaptosuccinic acid.*

Selective DMSA verification

Delayed DMSA scintigraphy was strongly selective rather than random. Compared with children without DMSA scintigraphy, those who underwent DMSA scintigraphy had longer fever

duration, higher maximum temperature, CRP, PCT, WBC, and uKIM-1, and were more likely to have abnormal ultrasound findings and pyuria (**Table 4**). After FDR correction, the strongest selection signals included CRP, PCT, WBC, uKIM-1, abnormal ultrasound, and pyuria.

In an exploratory multivariable model of the work-up mechanism, higher PCT, abnormal ultrasound, and longer fever duration remained independently associated with undergoing DMSA scintigraphy. An inverse-probability-of-verification sensitivity analysis produced an adjusted scar proportion of 41.4% but with a wide bootstrap interval (22.3-61.6%) and an effective weighted sample size of approximately 27; this unstable estimate was therefore not used as the primary prevalence estimate.

Variable	DMSA performed	No DMSA	p	BH-FDR q
Fever duration, days	2 (1-4)	1 (1-2)	0.015	0.026
Maximum temperature, °C	38.5 (38.1-39)	38.0 (37.5-38.58)	0.008	0.020
CRP, mg/dL	6.32 (2.65-15.61)	0.725 (0.30-2.31)	<0.001	<0.001
PCT, ng/mL	1.19 (0.21-3.67)	0.08 (0.048-0.22)	<0.001	<0.001
WBC, /µL	16,400 (12,500-24,000)	11,950 (7,703-15,700)	<0.001	0.001
uKIM-1, ng/mL	0.342 (0.139-0.577)	0.129 (0-0.255)	0.002	0.007
Abnormal ultrasound	21/45 (46.7%)	5/38 (13.2%)	0.002	0.007
Pyuria	31/45 (68.9%)	13/38 (34.2%)	0.002	0.007

Table 4. Selective performance of delayed DMSA scintigraphy; *Continuous variables are median (IQR) and categorical variables are n/N (%); This table describes the clinical work-up mechanism rather than disease causation; BH-FDR correction was applied across the broader*

displayed DMSA-selection comparison family in the prespecified sensitivity workbook; BH-FDR, Benjamini-Hochberg false discovery rate; CRP, C-reactive protein; DMSA, dimercaptosuccinic acid; IQR: interquartile range; PCT, procalcitonin; uKIM-1, urinary kidney injury molecule-1; WBC, white blood cells

Vesicoureteral reflux analyses

VCUG was available in 54 children. Nineteen (35.2%) had any VUR and 17 (31.5%) had high-grade VUR. Abnormal ultrasound was the most consistent anatomical signal for both outcomes, whereas biomarker associations were modest and did not survive FDR correction. These findings were similar when the three children with non-reflux "other" VCUG abnormalities were excluded from the control group.

Feature	Any VUR (19) vs control (35)	p / q	High-grade VUR (17) vs control (37)	p / q
Abnormal ultrasound	OR 4.29 (95% CI 1.31-14.03); Se 63.2%, Sp 71.4%	0.021 / —	OR 4.33 (95% CI 1.28-14.67); Se 64.7%, Sp 70.3%	0.020 / —
CRP, mg/dL	6.45 (1.53-13.04) vs 1.18 (0.42-4.43)	0.022 / 0.152	7.03 (0.74-14.59) vs 1.19 (0.48-4.49)	0.024 / 0.152
PCT, ng/mL	1.56 (0.20-4.69) vs 0.17 (0.06-1.30); n=48	0.115 / 0.305	1.89 (0.18-5.21) vs 0.20 (0.06-1.26); n=48	0.109 / 0.305

uKIM-1, ng/mL	0.280 (0.117-0.802) vs 0.171 (0.041-0.329); n=52	0.112 / 0.305	0.374 (0.139-0.911) vs 0.157 (0.033-0.328); n=52	0.031 / 0.157
uNGAL, ng/mL	1.751 (1.361-2.128) vs 1.513 (1.193-2.328); n=52	0.483 / 0.603	1.701 (1.334-1.988) vs 1.590 (1.207-2.424); n=52	0.960 / 0.960
uPTX3, ng/mL	4.455 (1.638-11.904) vs 3.136 (0-10.806); n=52	0.215 / 0.440	5.997 (3.235-13.865) vs 2.441 (0-9.926); n=52	0.045 / 0.157

Table 5. Clinical, ultrasound, and biomarker findings according to VUR status; *Values are median (IQR) unless otherwise stated; Primary any-VUR control group includes normal plus other non-reflux VCUG findings (high-grade VUR was grade III or higher); Sensitivity analyses excluding three "other" findings were similar (abnormal ultrasound OR 4.38 for any VUR and 4.40 for high-grade VUR); q values are BH-FDR-adjusted for the exploratory biomarker comparison family; ultrasound associations are shown with unadjusted Fisher exact p-values; BH-FDR, Benjamini-Hochberg false discovery rate; CRP, C-reactive protein; DMSA, dimercaptosuccinic acid; IQR: interquartile range; PCT, procalcitonin; Se, sensitivity; Sp, specificity; uKIM-1, urinary kidney injury molecule-1; uNGAL, urinary neutrophil gelatinase-associated lipocalin; uPTX3, urinary pentraxin-3; VUR, vesicoureteral reflux; VCUG, voiding cystourethrography.*

Exploratory biomarker cutoffs for kidney scarring

Youden-derived thresholds were explored to characterize sensitivity-specificity trade-offs rather than to define clinical decision limits. PCT at 2.10 ng/mL provided the most balanced systemic-

marker threshold (sensitivity 64.3%, specificity 77.8%), whereas the high-specificity CRP threshold identified very few scars. Urinary PTX3 and uPTX3/uCr yielded 100% observed sensitivity at their Youden thresholds but poor specificity and small negative-test denominators; the normalized PTX3 result was additionally unstable to zero-value handling. Therefore, none of these internally derived thresholds is suitable for clinical rule-in or rule-out use without external validation (**Table 6**).

Biomarker	n / scars	AUC (95% CI)	Youden cutoff	Sensitivity %	Specificity %	PPV %	NPV %
CRP	45 / 16	0.448 (0.272-0.636)	≥26.43 mg/dL	12.5	96.6	66.7	66.7
PCT	41 / 14	0.626 (0.407-0.823)	≥2.10 ng/mL	64.3	77.8	60.0	80.8
uKIM-1	44 / 16	0.606 (0.430-0.784)	≥0.608590	43.8	85.7	63.6	72.7
uNGAL	44 / 16	0.406 (0.254-0.576)	≥1.327345	75.0	35.7	40.0	71.4
uPTX3	44 / 16	0.610 (0.436-0.763)	≥0.967859	100.0	35.7	47.1	100.0
uKIM-1/uCr	30 / 12	0.606 (0.384-0.813)	≥0.049992	58.3	77.8	63.6	73.7
uNGAL/uCr	30 / 12	0.352 (0.167-0.597)	≥0.115349	58.3	44.4	41.2	61.5

uPTX3/uCr	30 / 12	0.727 (0.523-0.898)	≥0.030245	100.0	44.4	54.5	100.0

Table 6. Exploratory Youden cutoffs for DMSA-defined kidney scarring; *Cutoffs were selected and evaluated in the same DMSA-verified samples and are exploratory; AUC CIs are bootstrap estimates from the dedicated cutoff analysis. Positive predictive value and NPV apply only to the selected DMSA-verified subsets and are not population-level predictive values; The apparent uPTX3/uCr signal was attenuated when zero-coded uPTX3 values were excluded; AUC, area under the receiver operating characteristic curve; CI, confidence interval; CRP, C-reactive protein; DMSA, dimercaptosuccinic acid; NPV, negative predictive value; PCT, procalcitonin; PPV, positive predictive value uKIM-1, urinary kidney injury molecule-1; uNGAL, urinary neutrophil gelatinase-associated lipocalin; uPTX3, urinary pentraxin-3; uCr, urinary creatinine; VUR, vesicoureteral reflux; VCUG, voiding cystourethrography.*

Discussion

This prospective first fUTI cohort adds a deliberately conservative assessment of biomarker and imaging risk signals for delayed DMSA-defined kidney scarring. Four findings are most relevant. First, PCT discriminated scarring better than CRP in the same children, but its AUC remained only moderate. Second, no urinary biomarker provided a robust standalone signal; uPTX3/uCr was numerically the strongest but was sensitive to multiplicity and assay-limit handling. Third, non-E. coli infection was the strongest clinical correlate of scarring. Fourth, abnormal ultrasound was associated with both any and high-grade VUR, but its moderate sensitivity confirms that ultrasound should be viewed as a structural risk-stratification test rather than a definitive test for reflux.

The PCT findings are consistent with a substantial body of literature while also illustrating why a single cutoff cannot simply be transported across cohorts. In the individual-patient meta-analysis by Leroy et al., PCT outperformed CRP and leukocyte count for both acute pyelonephritis and late scarring; a threshold of 0.5 ng/mL was associated with late scarring but offered only moderate specificity [18]. Earlier meta-analysis likewise supported PCT for acute kidney parenchymal involvement, with important between-study heterogeneity [35]. More recently, a 2026 first-fUTI study reported better discrimination of acute DMSA lesions by PCT than CRP [36]. In our cohort, the internally optimal PCT threshold for late scarring was higher (2.10 ng/mL) and yielded 64.3% sensitivity and 77.8% specificity. The difference is clinically informative: biomarker thresholds depend on the target phenotype (acute parenchymal involvement versus permanent scar), case mix, timing, and verification strategy, and should not be treated as universal constants.

The urinary biomarker results were more heterogeneous. Lee et al. reported that urinary KIM-1 and NGAL were elevated in fUTI and that KIM-1 showed moderate discrimination for subsequent scarring [19], whereas Krzemień et al. found neither normalized nor absolute uNGAL or uKIM-1 useful for distinguishing DMSA-defined acute pyelonephritis in young children [20]. Our negative or weak findings for uKIM-1 and uNGAL therefore fall within the range of published results rather than contradicting a uniform literature. The 2026 meta-analysis focused on children with VUR similarly found only moderate pooled performance of urinary biomarkers, with NGAL/creatinine the most frequently studied marker but substantial heterogeneity [22].

Urinary PTX3 deserves separate consideration because our acute-phase design differs from the principal published pediatric scar study. Becerir et al. measured PTX3 in children with established kidney parenchymal scars after prior pyelonephritis and reported higher uPTX3 and PTX3/creatinine in scarred kidneys [21]. In contrast, we sampled urine before antibiotic

treatment during the index first fUTI and asked whether PTX3 predicted a later DMSA outcome. The nominal uPTX3/uCr AUC of 0.727 was therefore biologically interesting, but it did not survive FDR correction and fell to approximately 0.55 when zero-coded values were excluded. This strong dependence on lower-limit handling argues for prespecified LOD/LOQ rules, duplicate measurements, and harmonized urinary creatinine normalization before PTX3 can be evaluated as a reproducible prognostic marker.

The cutoff analysis reinforces the same message. Several thresholds looked attractive in isolation: uPTX3 and uPTX3/uCr had 100% observed sensitivity at their Youden thresholds, while a CRP threshold of 26.43 mg/dL had 96.6% specificity. However, these estimates arose from only 12-16 scar events per biomarker analysis, were optimized and evaluated in the same selected sample, and in some instances were supported by very small numbers of negative tests. High apparent sensitivity or NPV in this setting is therefore vulnerable to optimism and spectrum effects. The cutoffs should be viewed as candidate values for future validation, not as actionable thresholds for deciding whether to perform DMSA.

The VUR analyses add a clinically important anatomical dimension. Any VUR was present in 19/54 children who underwent VCUG and high-grade VUR in 17/54. Abnormal ultrasound increased the odds of any VUR by approximately fourfold and of high-grade VUR by a similar magnitude, but sensitivity remained around 63-65%. This is closely aligned with the updated 2026 AAP evidence synthesis: pooled RBUS sensitivity for VUR after a first UTI is about 50% and remains incomplete even for high-grade reflux [11]. The 2026 AAP guideline accordingly recommends RBUS to identify structural abnormalities or VUR-associated findings, not to diagnose VUR itself, and suggests against routine VCUG after a first fUTI when RBUS is normal while allowing targeted VCUG in higher-risk subgroups [10]. Acute DMSA abnormalities have also been associated with dilating VUR in young children with a first fUTI [37]. Our findings

support that distinction: an abnormal RBUS meaningfully raises anatomical risk, but a normal RBUS cannot exclude clinically relevant reflux.

This interpretation is also supported by broader imaging evidence. A 2023 systematic review of 9,170 children found abnormalities on kidney ultrasound after first fUTI in approximately one in five children, but clinically important findings that altered management in only a small minority [38]. Earlier work likewise demonstrated that ultrasonography has imperfect sensitivity for DMSA-defined kidney scarring [39]. In our cohort, ultrasound was more informative for VUR than for DMSA-defined scarring, emphasizing that RBUS and DMSA address different questions. DMSA detects cortical sequelae, whereas ultrasound primarily identifies anatomy and features that may change the pretest probability of VUR or other urinary tract abnormalities.

Non-E. coli infection was associated with nearly tenfold higher odds of scarring in the DMSA-verified subset. This observation is concordant with the updated AAP framework, in which non-E. coli infection is one of the clinical features that may justify VCUG after a first fUTI despite otherwise reassuring imaging [10], and with recent cohorts linking non-E. coli pathogens to scarring or clinically relevant urinary tract abnormalities [40,41]. In the young-infant cohort reported by Tham et al., scarring was associated with elevated PCT, non-E. coli infection, hydronephrosis, and particularly VUR [41]. Non-E. coli infection may therefore function as an integrated marker of altered anatomy, host susceptibility, antimicrobial exposure, and infection complexity rather than as a simple causal determinant.

Vesicoureteral reflux itself remains an established risk modifier for scarring, particularly at higher grades. The classic systematic review after first UTI found that VUR increased scar risk and that grade III or higher reflux conferred additional risk [5]. In the RIVUR population, baseline and follow-up DMSA demonstrated that kidney scarring clustered in children with higher-risk reflux phenotypes even though antimicrobial prophylaxis reduced recurrence more clearly than

new scarring [42,43]. More recent first-fUTI cohorts and guideline-appraisal studies likewise identify high-grade VUR as a major scar-associated factor [40,41,44,45]. Our VCUG analyses should nevertheless be interpreted cautiously because VCUG, like DMSA, was clinically selective.

The central methodological limitation is partial verification bias. DMSA was obtained in only 54.2% of the cohort, and children selected for DMSA had higher PCT, CRP, WBC, uKIM-1, fever severity, pyuria, and more abnormal ultrasound findings. This real-world work-up pattern can distort associations because the outcome is observed preferentially in children whose baseline variables already suggested greater risk. It also provides a plausible explanation for paradoxical within-subset findings such as shorter fever duration or lower WBC among scar-positive children. The observed 35.6% scar proportion is therefore a verified-subgroup proportion, not the cohort incidence. The wide inverse-probability-weighted estimate further shows that statistical correction cannot compensate fully for a small, selectively verified dataset.

The study nevertheless has important strengths. Enrollment was prospective and restricted to a first fUTI, urine for research biomarkers was obtained before antibiotics, systemic and urinary markers were measured in parallel, urinary creatinine-normalized analyses were prespecified, and delayed DMSA was used as the scar reference standard. We explicitly examined the DMSA selection mechanism, urine-collection sensitivity, multiple testing, and PTX3 zero-value handling. These features improve interpretability of both positive and negative findings and reduce the risk of presenting an internally optimized biomarker as prematurely clinically useful.

Limitations include the single-center and infant-dominant case mix, only 16 scar events, selective DMSA and VCUG, smaller denominators for creatinine-normalized markers, and uncertainty regarding assay-limit encoding for PTX3. Delayed DMSA without a systematic acute or baseline scan cannot always distinguish an acquired post-infectious scar from congenital

dysplasia. In addition, the study was not sized for development of a stable multivariable prediction model; penalized models remain hypothesis-generating. These limitations are typical of the biomarker literature, where small samples, heterogeneous assays, and incomplete outcome verification continue to limit transportability [15,17,22].

The most defensible next step is therefore not another single-marker study, but a prospectively powered validation study with standardized pre-antibiotic sampling, explicit assay LOD/LOQ handling, systematic or protocol-driven delayed DMSA, and prespecified handling of VCUG. Candidate models should start with readily available variables - organism profile, PCT, age, fever course, and ultrasound - and then test whether urinary biomarkers add incremental discrimination, calibration, and clinical net benefit. External validation should precede any use of a biomarker or cutoff to defer DMSA or select children for invasive imaging.

Conclusions

After a first pediatric fUTI, PCT discriminated delayed DMSA-defined kidney scarring better than CRP, but its standalone performance and internally derived cutoff were insufficient for clinical decision-making. Absolute uKIM-1, uNGAL, and uPTX3 were not robust predictors of scarring, and the apparent uPTX3/uCr signal was unstable to multiplicity and assay-limit sensitivity analyses. Non-E. coli infection was the strongest scar-associated clinical feature. Abnormal ultrasound was associated with both any and high-grade VUR but lacked sufficient sensitivity to exclude reflux. Larger prospective cohorts with protocol-driven outcome verification and external validation are required before biomarker-guided DMSA or VCUG strategies can be recommended.

Statements and Declarations

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Ethics approval: The study was approved by the Assembly/Ethics authority of the School of Medicine, Aristotle University of Thessaloniki (approval 30 May 2023; registration no. 5057; study no. 108/2023).

Consent to participate: Written informed consent was obtained from parents or legal guardians in accordance with the approved protocol.

Data availability: De-identified data may be made available from the corresponding author upon reasonable request, subject to institutional and ethics restrictions.

Author contributions: Nikolaos Gkiourtzis: conception and design of the work, analysis, and interpretation of data, drafted the work, approved the version to be published, agreed to be accountable for all aspects of the work; **Panagiota Michou:** analysis and interpretation of data, revised the work critically, approved the version to be published, agreed to be accountable for all aspects of the work; **Anastasia Stoimeni:** analysis and interpretation of data, revised the work critically, approved the version to be published, agreed to be accountable for all aspects of the work; **Konstantinos Cheirakis:** analysis and interpretation of data, revised the work critically, approved the version to be published, agreed to be accountable for all aspects of the work; **Vera Karatisidou:** analysis and interpretation of data, revised the work critically, approved the version to be published, agreed to be accountable for all aspects of the work; **Vasileios Liakos:** analysis and interpretation of data, revised the work critically, approved the version to be published, agreed to be accountable for all aspects of the work; **Areti Kourti:** analysis and interpretation of data, revised the work critically, approved the version to be published, agreed to be accountable for all aspects of the work; **Charalampos Antahopoulos:**

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Supplementary Figure 1

Study flow chart; DMSA, technetium-99m dimercaptosuccinic acid; fUTI, febrile urinary tract infection; PCT, procalcitonin; uCr, urinary creatinine; VCUG, voiding cystourethrography; VUR, vesicoureteral reflux

Supplementary Files

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