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Review Article

Diagnostic accuracy of serum and urinary biomarkers for renal scarring in children with vesicoureteral reflux: A systematic review and meta-analysis

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ABSTRACT

Background: Renal scarring (RS) is a significant long-term complication of vesicoureteral reflux (VUR), traditionally diagnosed by dimercaptosuccinic acid (DMSA) scintigraphy—a costly imaging modality involving ionizing radiation. Non-invasive serum and urinary biomarkers have been proposed as alternative diagnostic tools. This systematic review and meta-analysis evaluated the diagnostic accuracy of these biomarkers for detecting RS in children with VUR.

Methods: A comprehensive search was conducted in MEDLINE, EMBASE, Scopus, Web of Science, LILACS, Cochrane Library, and ProQuest through July 2024. Studies including children (0–18 years) with VUR confirmed by voiding cystourethrography and using DMSA scintigraphy as the reference standard were eligible. Data extraction and quality assessment (QUADAS-2) were independently performed by two reviewers. Pooled sensitivity and specificity were estimated using a bivariate random-effects model.

Results: Ten studies met inclusion criteria; eight were included in meta-analyses. Serum biomarkers showed pooled sensitivity of 0.73 (95 % CI: 0.63–0.81) and specificity of 0.74 (95 % CI: 0.52–0.88). Urinary biomarkers had pooled sensitivity of 0.65 (95 % CI: 0.32–0.88) and specificity of 0.71 (95 % CI: 0.58–0.82). NGAL adjusted for creatinine (NGAL/Cr) was the most frequently studied urinary biomarker, with sensitivity of 0.72 (95 % CI: 0.58–0.83) and specificity of 0.63 (95 % CI: 0.55–0.70). Considerable heterogeneity was observed.

Conclusions: Selected serum and urinary biomarkers—particularly NGAL and cystatin C—demonstrate moderate diagnostic accuracy for RS in children with VUR. These non-invasive biomarkers may complement DMSA scintigraphy, although further high-quality studies are needed to confirm their clinical utility.

1. Introduction

Urinary tract infection (UTI) is among the most common bacterial infections in childhood, with an estimated incidence of up to 8 % in children under 11 years of age [1]. Vesicoureteral reflux (VUR) is a major risk factor for UTI and its complications [2], with an overall prevalence of approximately 1.6 % and present in 30–50 % of children with recurrent UTIs. A key long-term consequence of VUR is renal scarring (RS), which results from recurrent pyelonephritis and is associated with progressive inflammation and immune-mediated injury. Renal scars can lead to proteinuria, impaired growth, hypertension, and chronic kidney disease [3,4].

Technetium-99m dimercaptosuccinic acid (DMSA) renal scintigraphy remains the gold standard for detecting RS. Although reliable, this imaging modality is expensive, exposes patients to ionizing radiation, and requires specialized facilities and trained personnel. These limitations highlight the need for accessible, cost-effective, and non-invasive diagnostic alternatives [5,6].

In recent years, several serum and urinary biomarkers have been investigated as potential tools for detecting renal injury and fibrosis. Serum biomarkers include components of the endothelial

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glycocalyx (eGC)—such as heparan sulfate and syndecan-1—which reflect endothelial damage [6]. Cystatin C, a low-molecular-weight protein freely filtered by the glomerulus, has also been studied as an alternative to serum creatinine for kidney function assessment and may correlate with RS in children with VUR [7].

Urinary biomarkers encompass pentraxin-3 (PTX3), a pro-inflammatory molecule involved in renal fibrosis [8,9]; connective tissue growth factor (CTGF), promoting fibroblast proliferation and extracellular matrix deposition [10]; interleukins 6 and 8 (IL-6, IL-8), elevated during acute UTIs in children with VUR [11]; kidney injury molecule-1 (KIM-1), a transmembrane glycoprotein expressed in injured proximal tubular cells [12,13]; liver-type fatty acid-binding protein (L-FABP), associated with tissue hypoxia and chronic ischemic damage [14]; transforming growth factor-beta 1 (TGF-β1), a profibrotic cytokine [15]; vascular endothelial growth factor (VEGF), linked to inflammation and proteinuria in reflux nephropathy [16]; and neutrophil gelatinase-associated lipocalin (NGAL), a protein induced by lipopolysaccharides and highly expressed in both acute and chronic kidney injury [17–19].

These biomarkers offer promising avenues for early diagnosis and longitudinal monitoring of RS in pediatric patients with VUR. However, no consensus has been reached regarding their diagnostic performance. This systematic review and meta-analysis aimed to evaluate the diagnostic accuracy of both serum and urinary biomarkers for detecting renal scarring in children with VUR, using DMSA renal scintigraphy as the reference standard.

2. Methods

This systematic review and meta-analysis were conducted following the Cochrane Handbook for Systematic Reviews of Diagnostic Test Accuracy and the PRISMA-DTA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Diagnostic Test Accuracy) guidelines [20]. The study protocol was registered in the PROSPERO database (CRD251606).

2.1. Eligibility criteria

We included diagnostic accuracy studies (cross-sectional or cohort; prospective or retrospective) evaluating serum and/or urinary biomarkers for detecting renal scarring (RS) in children aged 0–18 years with vesicoureteral reflux (VUR) confirmed by voiding cystourethrography (VCUG). The reference standard for RS was 99mTc-dimercaptosuccinic acid (DMSA) renal scintigraphy [5].

Studies were eligible if they reported, or allowed calculation of, true positives (TP), false positives (FP), true negatives (TN), and false negatives (FN), enabling construction of 2 × 2 contingency tables or calculation of sensitivity and specificity.

2.2. Search strategy

A comprehensive search was performed in six electronic databases: MEDLINE (via PubMed), EMBASE, Scopus, Web of Science, LILACS, and the Cochrane Library, with no restrictions on language, publication date, or country. The most recent search was completed in July 2024.

The search strategy combined controlled vocabulary (e.g., MeSH, Emtree) and free-text terms related to “vesicoureteral reflux,” “renal scarring,” and “biomarkers.”

2.3. Study selection and data extraction

Titles and abstracts were screened independently by two reviewers. Full-text articles were also independently assessed, and data were extracted by two reviewers, with disagreements resolved by a third reviewer.

Extracted data included study characteristics (author, year, country, design), population demographics, type of biomarker, assay methods, index and reference tests, and diagnostic performance metrics. Authors were contacted for clarification when relevant data were missing or unclear.

2.4. Risk of bias assessment

The methodological quality of included studies was evaluated using the QUADAS-2 tool (Quality Assessment of Diagnostic Accuracy Studies–2) [21], which assesses risk of bias in four domains: patient selection, index test, reference standard, and flow and timing. Applicability concerns were also evaluated. Two reviewers performed assessments independently and reached consensus through discussion.

2.5. Statistical analysis

Meta-analyses were conducted using a bivariate random-effects model to pool sensitivity and specificity for each biomarker. Summary receiver operating characteristic (SROC) curves were constructed when appropriate. Heterogeneity was assessed using the I^2 statistic and visual inspection of forest plots.

All analyses were performed using Review Manager (RevMan version 5.4.1, Cochrane Collaboration) and MetaDTA software (University of Leicester, UK).

Artificial intelligence tools were not used; all data extraction, analysis, and interpretation were conducted manually by the authors.

3. Results

3.1. Study selection

A total of 1426 records were identified through database searches. After removal of 369 duplicates, 1057 studies remained for title and abstract screening. Of these, 34 full-text articles were assessed for eligibility. Ultimately, 10 studies met the inclusion criteria for the systematic review, and 8 were included in the meta-analysis. The study selection process is summarized in the PRISMA flow diagram (Fig. 1) [20].

3.2. Study characteristics

The included studies were published between 2010 and 2022, originating from Iran [22], Turkey [23–27,29,30], Japan [26], India [28], and Ukraine, with a total of 924 children with confirmed VUR. Study designs comprised both case–control and cohort studies.

Biomarkers assessed included serum cystatin C [30] and components of the endothelial glycocalyx, such as heparan sulfate and syndecan-1 [24]. Urinary biomarkers included pentraxin-3 (PTX3) [23], interleukins 6 and 8 (IL-6, IL-8) [25], connective tissue growth factor (CTGF) [27], transforming growth factor-beta 1 (TGF-β1) and vascular endothelial growth factor (VEGF), kidney injury molecule-1 (KIM-1), liver-type fatty acid-binding protein (L-FABP) [29], and neutrophil gelatinase-associated lipocalin (NGAL) [22,26,28,29]. Several studies reported values normalized to urinary creatinine (e.g., NGAL/Cr, CTGF/Cr, L-FABP/Cr).

3.3. Risk of bias assessment

Methodological quality, assessed using QUADAS-2 [21], indicated a high risk of bias in most studies, particularly in patient

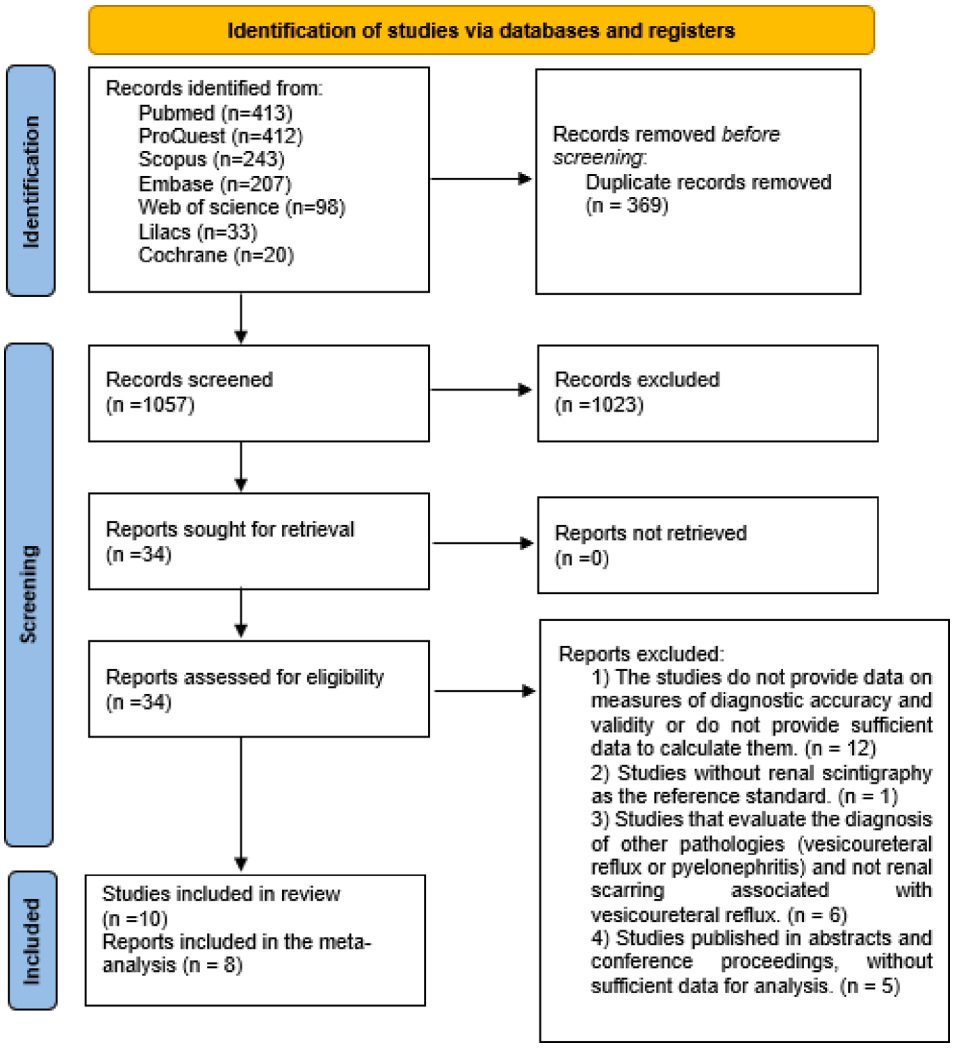

Fig. 1. PRISMA 2020 flow diagram illustrating the study selection process. Boxes indicate the number of records excluded at each stage and the reasons for exclusion.

selection, index test application, and flow and timing. Only one study demonstrated low risk of bias for the reference standard domain. Applicability concerns were generally low across all domains. Visual summaries of risk of bias and applicability judgments are presented in Supplementary Figs. 1 and 2.

3.4. Meta-analysis of diagnostic accuracy

3.4.1. Urinary biomarkers

Eight studies [23–30] were included in the meta-analysis of urinary biomarkers. Pooled sensitivity and specificity were 0.65 (95 % CI: 0.32–0.88) and 0.71 (95 % CI: 0.58–0.82), respectively, with substantial heterogeneity ($I^2 = 86$ % for sensitivity; $I^2 = 78$ % for specificity). Heterogeneity likely reflects differences in biomarker types, population characteristics, and cutoff values. Diagnostic estimates for individual studies are shown in Supplementary Fig. 3.

3.4.2. Urinary biomarkers adjusted by creatinine

Subgroup analysis of urinary biomarkers normalized to creatinine (e.g., NGAL/Cr, CTGF/Cr) yielded pooled sensitivity of 0.70 (95 % CI: 0.56–0.81) and specificity of 0.62 (95 % CI: 0.46–0.76), with high heterogeneity ($I^2 = 77$ % for sensitivity; $I^2 = 82$ % for specificity; $p < 0.01$), as illustrated in Supplementary Fig. 4. NGAL/Cr and CTGF/Cr demonstrated moderate diagnostic performance amid substantial heterogeneity.

3.4.3. Serum biomarkers

Two studies [24,30] assessed serum biomarkers for RS detection. Pooled sensitivity was 0.73 (95 % CI: 0.63–0.81; $I^2 = 0$ %), and pooled specificity was 0.74 (95 % CI: 0.52–0.88; $I^2 = 82$ %, $p < 0.01$). Biomarkers included heparan sulfate and syndecan-1 [24], and cystatin C [30]. These results are illustrated in Fig. 2. Serum markers showed moderate-to-high diagnostic accuracy, with limited heterogeneity in sensitivity and greater variability in specificity.

3.5. NGAL adjusted by creatinine (NGAL/Cr)

Three studies [26,28,29] specifically evaluated NGAL/Cr. Pooled sensitivity was 0.72 (95 % CI: 0.58–0.83; $I^2 = 62$ %), and pooled specificity was 0.63 (95 % CI: 0.55–0.70; $I^2 = 0$ %). These results suggest consistent diagnostic performance for NGAL/Cr as a non-invasive marker of renal scarring, with corresponding forest plots shown in Fig. 3.

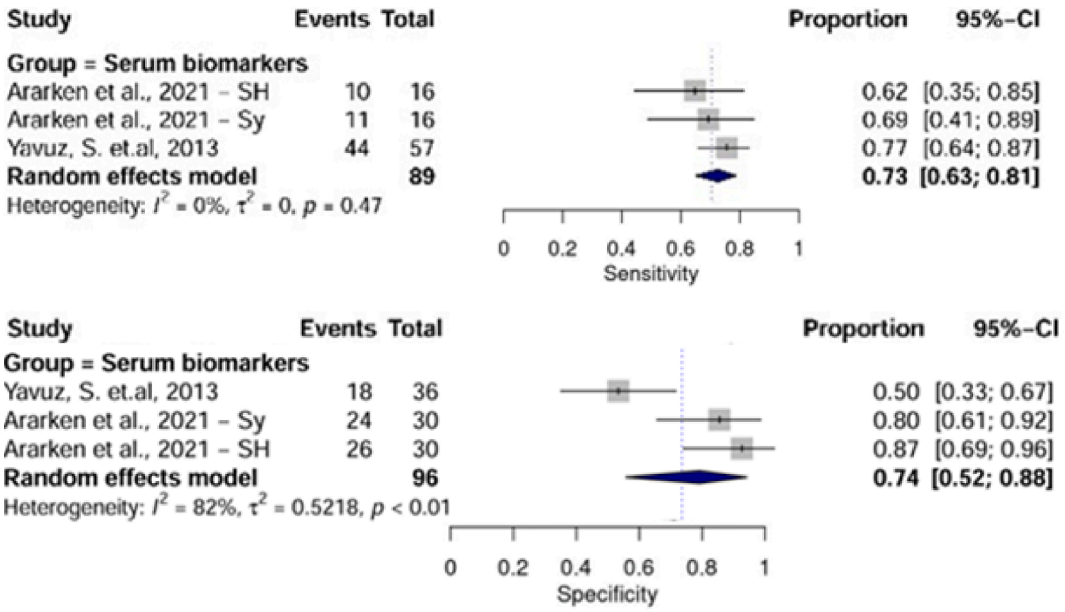

Fig. 2. Forest plot showing sensitivity and specificity of serum biomarkers.

3.6. Quantitative summary tables

Extracted diagnostic data for included studies are detailed in Table 1 (serum biomarkers) and Table 2 (urinary biomarkers, including creatinine-adjusted markers).

4. Discussion

This systematic review and meta-analysis evaluated the diagnostic accuracy of serum and urinary biomarkers for detecting renal scarring (RS) in children with vesicoureteral reflux (VUR). Our findings indicate that both serum and urinary biomarkers—particularly urinary NGAL and serum cystatin C—demonstrate moderate sensitivity and specificity, suggesting their potential as non-invasive diagnostic tools. However, methodological limitations and substantial heterogeneity among studies preclude definitive conclusions.

Pooled estimates for urinary biomarkers yielded a sensitivity of 0.65 and specificity of 0.71 (Supplementary Fig. 3). When normalized to urinary creatinine, these values slightly improved to a sensitivity of 0.70 and specificity of 0.62 (Supplementary Fig. 4). Among these markers, NGAL/Cr showed the most consistent performance, with a pooled sensitivity of 0.72 (95 % CI: 0.58–0.83) and specificity of 0.63 (95 % CI: 0.55–0.70) across three studies [26,28,29] (Fig. 3).

Serum biomarkers demonstrated moderate diagnostic accuracy, with pooled sensitivity of 0.73 and specificity of 0.74, particularly for heparan sulfate and syndecan-1 (components of the endothelial glycocalyx) [24] and cystatin C [30] (Fig. 2, Table 1). These results suggest that serum markers may perform as well as, or in some cases better than, urinary biomarkers in specific clinical scenarios.

Inflammatory cytokines such as IL-6 and IL-8, evaluated in one study [25], showed elevated urinary levels in children with RS,

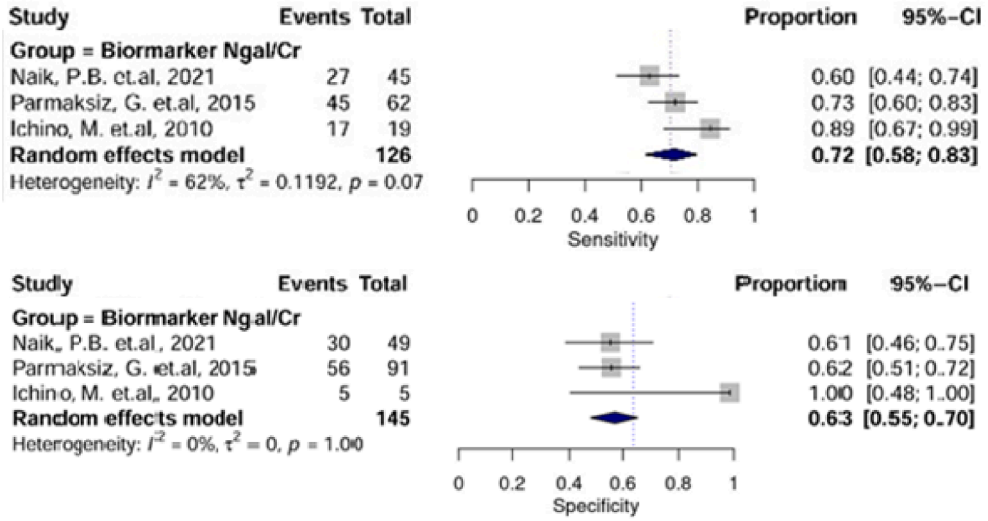

Fig. 3. Forest plot of urinary NGAL adjusted by creatinine (NGAL/Cr).

Table 1
Diagnostic accuracy of serum biomarkers, including sensitivity, specificity, and sample sizes.

Estudo Autor/ano	Biomarcador	TP	FP	TN	FN	N° affected	N° not affected	Sensitivity	Especificity	PPV	NPV	Accuracy
Yavuz, S. et al., 2013	Cistatina C	44	18	18	13	57	36	0,77	0,5	0,709	0,58	0,71
Akarken et al., 2021	Sulfato de heparan	19	8	52	11	30	60	0,63	0,87	0,703	0,825	0,784
	Syndecan-1	21	12	48	9	30	60	0,7	0,8	0,634	0,842	0,772

Table 2
Diagnostic accuracy of urinary biomarkers, including creatinine-adjusted markers. Decimal points are standardized.

Study Author/year	Biomarker	TP	FP	TN	FN	N° affected	N° not affected	Sensitivity	Especificity	PPV	NPV	Accuracy
Gokce, I. et al., 2010	IL- 8/Cr	51	39	24	09	60	54	0,85	0,44	0,629	0,723	0,66
Ichino, M. et al., 2010	uNGAL/uCr	17	0	5	2	19	5	0,895	1	1	0,714	0,947
Parmaksiz, G. et al., 2016	uL-FABP/Cr	48	37	54	14	62	91	0,77	0,59	0,564	0,794	0,641
	uNGAL/Cr	45	35	56	17	62	91	0,73	0,61	0,562	0,767	0,74
Gültekin, N.D. et al., 2019	uCTFG/Cr	21	12	74	25	46	86	0,46	0,855	0,636	0,747	0,646
	uCTFG	40	40	46	6	46	86	0,87	0,532	0,5	0,884	0,722
Makieieva, N.I. et al., 2020	TGF - b1	35	11	91	4	39	102	0,885	0,891	0,76	0,957	0,906
	VEGF	4	26	76	35	39	102	0,1	0,744	0,133	0,684	0,932
Naik, P.B. et al., 2022	uKIM - 1	24	20	29	21	45	49	0,533	0,592	0,545	0,58	0,523
	uKIM-1/Cr	22	34	15	23	45	49	0,489	0,306	0,392	0,394	0,337
	uNGAL	32	14	35	13	45	49	0,71	0,714	0,695	0,729	0,769
	uNGAL/Cr	27	19	30	18	45	49	0,6	0,612	0,587	0,625	0,611

reflecting their role in inflammation and fibrosis. Similarly, urinary CTGF and TGF-β1, involved in fibrogenesis, showed promising diagnostic performance [27], although findings were inconsistent. VEGF, a promoter of angiogenesis and proteinuria in reflux nephropathy [16], exhibited excellent sensitivity and specificity in a single study (100 % and 93.2 %, respectively), but this result remains unreplicated.

The risk of bias across included studies was generally high (Supplementary Figs. 1 and 2), particularly in patient selection, index test application, and flow/timing domains. Most studies lacked blinding and clearly defined thresholds for biomarker positivity. These factors may have influenced diagnostic performance and limit comparability across studies.

Compared with previous reviews, our study applied more stringent eligibility criteria, including exclusive use of DMSA scintigraphy as the reference standard and urographically confirmed VUR, thereby enhancing internal validity. Notably, this is the first meta-analysis to evaluate biomarker performance specifically in children with VUR using DMSA as the gold standard. Our findings are consistent with prior reviews highlighting NGAL and KIM-1 as promising markers of renal injury [18,19,21].

It is important to note that serum and urinary biomarkers are most informative during acute renal injury. Their utility in detecting established or chronic scars remains limited. Consequently, 99mTc-DMSA scintigraphy continues to be the reference standard for diagnosing renal scarring, despite its limitations such as radiation exposure, intravenous access requirements, and limited availability. Our results suggest that biomarkers may serve as complementary tools, potentially reducing the need for DMSA scans in follow-up or screening contexts, but cannot replace DMSA for late scar evaluation.

4.1. Limitations

Several limitations should be considered. First, most studies were small and single-center, limiting generalizability. Second, methodological quality was suboptimal, with high risk of bias in patient selection, index test blinding, and timing of assessments. Third, substantial heterogeneity existed, particularly for urinary biomarkers, due to differences in assay methods, cut-off values, age groups, and disease severity. Finally, the limited number of studies per biomarker restricted subgroup analyses and exploration of heterogeneity sources.

5. Conclusions

DMSA scintigraphy remains the gold standard for diagnosing renal scarring in children with VUR. Nonetheless, selected serum and urinary biomarkers—particularly NGAL and cystatin C—demonstrate moderate diagnostic accuracy and represent promising non-invasive alternatives. These markers may complement, and in some settings reduce the reliance on, DMSA, particularly for follow-up and screening. Further high-quality, multicenter diagnostic accuracy studies are warranted to validate these findings and determine optimal thresholds and biomarker combinations for clinical application.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jpedsurg.2025.162733.

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