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THE ROLE OF PROCALCITONIN IN THE EARLY DETECTION OF URINARY TRACT INFECTIONS WITH RENAL PARENCHYMAL INVOLVEMENT IN CHILDREN

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ABSTRACT

Background: Urinary tract infections (UTIs) are common childhood infections that may involve the renal parenchyma followed by late scarring. Early diagnosis and management of these infections can prevent renal scarring. Currently, dimercaptosuccinic acid (DMSA) scanning is the clinical gold standard to identify renal scarring but is not routinely performed. A more accessible assay could therefore prove useful. Thus, we aimed to evaluate the sensitivity and specificity of procalcitonin (PCT) in comparison with erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), using DMSA scan as reference, in the early detection of renal parenchymal involvement in children. **Methods:** In this cross-sectional study, 104 patients aged 1 month to 18 years, admitted to Bandar Abbas Pediatric Hospital from 2012 to 2015, due to their first episode of UTI were evaluated. UTI was confirmed by urine culture. Serum PCT, CRP, ESR and leukocyte count (LC) were measured before the initiation of antibiotic therapy. DMSA scan was performed during the first week of hospitalization and was considered as a reference for the detection of renal scarring. The receiver operating characteristic (ROC) curve was used to determine the sensitivity and specificity of the biomarkers for the detection of renal parenchymal involvement. **Results:** Mean PCT, CRP, ESR and LC of patients with parenchymal involvement were significantly higher compared to those without parenchymal involvement ($P<0.001$). PCT ≥1 ng/ml, CRP ≥1.5 mg/L, and ESR ≥30 mm/h were 100% sensitive for the early detection of renal parenchymal involvement. Their specificity was 88.3%, 100%, and 97.1%, respectively. **Conclusions:** Serum PCT, CRP and ESR are all strong markers for the early detection of renal parenchymal involvement in UTI. However, the specificity of CRP is higher than PCT and ESR.

KEYWORDS: urinary tract infection, renal scar, procalcitonin.

INTRODUCTION

As one of the most common childhood infections, urinary tract infection (UTI) has an incidence of 0.7-2.7% in the first year of life.[1,2] When UTI involves the renal parenchyma, it is called upper UTI (UUTI) or pyelonephritis.[3] Since APN can lead to renal scarring, which in turn can later result in hypertension, renal insufficiency, and end-stage renal disease, timely treatment of UTI is of utmost importance in children.[4]

Dimercaptosuccinic acid (DMSA) scan is the gold standard for the detection of renal parenchymal involvement; however, it has some limitations, including irradiation exposure, availability, and cost.[5,6] Several urine and serum biomarkers, such as C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), procalcitonin (PCT), leukocyte esterase, interleukins, D-dimer, and plasma neutrophil gelatinase-associated lipocalin have been evaluated for the diagnosis of UTI.[7-9] PCT is considered a reliable biomarker for the diagnosis of bacterial infection, owing to its rapid production after bacterial infection and high specificity.[10,11] Also, serum PCT has been associated with renal parenchymal injury.[11-13]

Using DMSA scan results as reference, we aimed to evaluate the sensitivity and specificity of PCT in comparison with ESR and CRP for the detection of renal parenchymal involvement in children.

METHODS

Participants and study design

This study received ethics approval from the Ethics Committee of Hormozgan University of Medical Sciences. Written informed consent was obtained from the parents/guardians of the patients. This cross-sectional study included pediatric patients aged 1 months to 18 years admitted to Bandar Abbas Children's Hospital, Bandar Abbas, Iran, from 2012 to 2015, due to their first

episode of UTI. Patients with a history of UTI were excluded from the study.

Urine samples were collected using one of these four methods: suprapubic aspiration (SPA), catheterization, urine bag, and mid-stream. In patients with samples collected using urine bags, negative results were interpreted as sterile urine; however, in case of positive results in these patients, another method of urine collection was applied to confirm the results. All urine specimens were cultured using the standard method. Urine cultures were considered positive if the colony-forming unit (CFU)/ml was $>10^4$ in the catheterization method, $>10^5$ in the mid-stream and urine bag methods, and >1000 in SPA. Patients with a positive urine culture were admitted to the hospital. Upon admission and before the initiation of antibiotics, random venous blood samples were collected from all the patients, in which PCT (using the electrochemiluminescence device and the Roche kit, Roche Diagnostics, Germany), CRP (using the COBAS INTEGRA® 400 plus analyzer and the Roche kit, Roche Diagnostics, Germany), and ESR (using the ESR reader device), and leukocyte count (LC) (using the XS-800i flowcytometry device, Sysmex, Denmark) were measured.

All patients were evaluated with respect to clinical presentations, such as fever (temperature >38°C), nausea, vomiting, diarrhea, and anorexia. Also, PCT ≥1 ng/ml, CRP ≥1.5 mg/L, and ESR ≥30 mm/h were regarded as positive. All patients underwent DMSA scanning within the first week of hospital admission, whose results were considered the gold standard and reference for renal parenchymal involvement. Patients were divided into two groups based on the results of the DMSA scan (positive/negative). Also, based on their clinical symptoms, patients were divided into two groups: UUTI and lower UTI (LUTI).

Data analysis

We used the Statistical Package for the Social Sciences (SPSS) software (version 26.0, Armonk, NY: IBM Corp., USA) for data analysis. Quantitative variables were described using means and standard deviations. Qualitative variables were described using frequencies and percentages.

The chi-squared test was used for the comparison of qualitative variables and the independent t-test for quantitative variables (based on the results of the Kolmogorov-Smirnov normality test). Also, by taking DMSA results as reference, the receiver operating characteristic (ROC) curves of ESR, CRP, and PCT were drawn to determine the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and the area under the curve (AUC) for the detection of renal parenchymal involvement. The Kappa coefficient was used to determine the agreement between any of these markers with DMSA results. P-values <0.05 were regarded as statistically significant.

RESULTS

Of the 104 children included in this study with a mean age of 5.12 ± 2.62 months, 75 (72.1%) were female and 29 (27.9%) were male. Patients in the UUTI group were significantly older than those in the LUTI group (P<0.001). There was no difference between patients with UUTI and LUTI regarding gender (P=0.076) (Table 1).

Positive DMSA and all clinical presentations were significantly higher in patients with UUTI. Moreover, mean serum PCT, CRP, ESR, and LC were significantly higher in the UUTI group compared to the LUTI group (Table 2). The frequency of positive PCT, CRP, and ESR, as well as leukocytosis was significantly higher in patients with positive DMSA results (Table 3).

Figure 1 demonstrates the ROC curves of PCT ≥1 ng/ml, CRP ≥1.5 mg/L, and ESR ≥30 mm/h for the detection of renal parenchymal involvement (positive DMSA). Accordingly, the calculated sensitivity, specificity, PPV, NPV, and AUC are shown in Table 4. CRP ≥1.5 mg/L was the best predictor of renal parenchymal involvement, followed by ESR, and PCT. Nevertheless, all three biomarkers at the aforementioned cut-offs were appropriate for the detection of such involvement.

Table 1: Comparison of demographics between patients with UUTI and LUTI.

Variables	Total (n=104)	UUTI (n=53)	LUTI (n=51)	P-value*
Age (months) mean ± SD	5.12 ± 2.62	6.31 ± 2.76	3.91 ± 1.80	<0.001
Age groups N (%)				
1-5 months	64 (61.5)	24 (45.3)	40 (78.4)	0.002†
6-10 months	31 (29.8)	23 (43.4)	8 (15.7)	
11-15 months	9 (8.7)	6 (11.3)	3 (5.9)	
Gender N (%)				
Male	29 (27.9)	11 (20.8)	18 (35.3)	0.076†
Female	75 (72.1)	42 (79.2)	33(64.7)	

Abbreviations: N, number; SD, standard deviation; UUTI, upper urinary tract infection; LUTI, lower urinary tract infection.

*Analyzed by the independent t-test.

†Analyzed by the chi-squared test.

Table 2: Comparison of DMSA results, PCT, ESR, CRP, LC, and clinical presentations between patients with UUTI and LUTI.

Variables	Total (n=104)	UUTI (n=53)	LUTI (n=51)	P-value*
DMSA results N (%)				
Positive	36 (34.6)	36 (67.9)	0 (0.0)	<0.001
Negative	68 (65.4)	17 (32.1)	51 (100.0)	
PCT (ng/ml) mean ± SD	1.47 ± 1.10	2.05 ± 1.05	0.66 ± 0.62	<0.001†
ESR (mm/h) mean ± SD	26.80 ± 19.87	40.41 ± 12.56	12.66 ± 1.82	<0.001†
CRP (mg/L) mean ± SD	1.04 ± 1.2	1.86 ± 1.12	0.20 ± 0.40	<0.001†
LC (/µl) mean ± SD	9516.43 ± 3802.98	12111.30 ± 2807.00	6819.60 ± 2653.70	<0.001†
Fever N (%)	54 (51.9)	53 (100.0)	1 (2.0)	<0.001
Nausea N (%)	59 (56.7)	35 (66.0)	24 (47.1)	0.039
Vomiting N (%)	73 (70.2)	45 (84.9)	28 (54.9)	0.001
Diarrhea N (%)	36 (34.6)	41 (77.4)	27 (52.9)	0.008
Anorexia N (%)	58 (55.8)	39 (73.6)	19 (37.3)	<0.001

Abbreviations: N, number; SD, standard deviation; UUTI, upper urinary tract infection; LUTI, lower urinary tract infection; DMSA, dimercaptosuccinic acid; PCT, procalcitonin; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; LC, leukocyte count.
*Analyzed by the chi-squared test.
†Analyzed by the independent t-test.

Table 3: Correlation between DMSA results, PCT, ESR, CRP, and LC.

Variables	Positive DMSA (n=36)	Negative DMSA (n=68)	P-value*
Positive PCT	36 (100.0)	42 (61.8)	<0.001
Positive CRP	19 (583.3)	0 (0.0)	<0.001
Positive ESR	36 (100.0)	37 (54.4)	<0.001
Leukocytosis	36 (100.0)	31 (45.6)	<0.001

Abbreviations: N, number; DMSA, dimercaptosuccinic acid; PCT, procalcitonin; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; LC, leukocyte count.
*Analyzed by the chi-squared test.

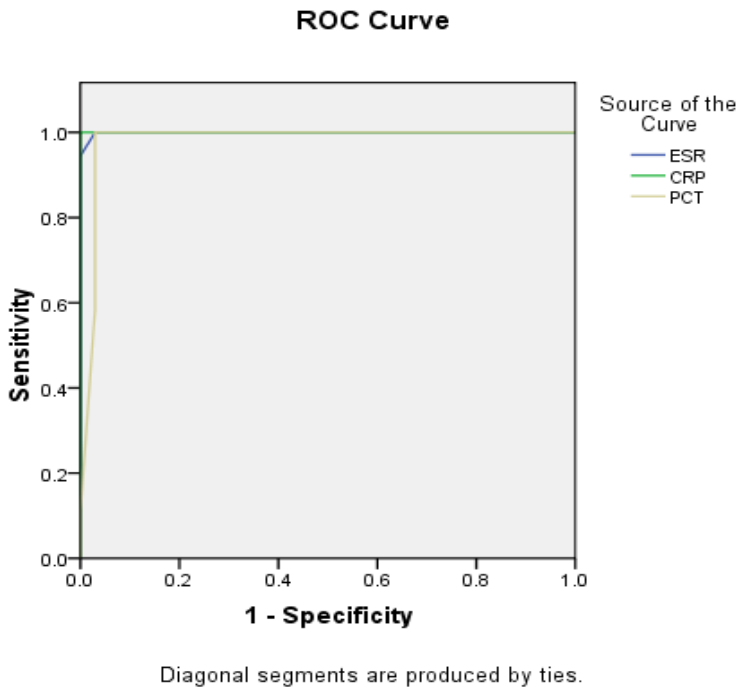

Figure 1: Receiver operating characteristic (ROC) curves of ESR, CRP, and PCT for the detection of renal parenchymal involvement.

Table 4: Diagnostic performance of ESR, CRP, and PCT for the detection of renal parenchymal involvement.

Variables	Sensitivity (95% CI)	Specificity (95% CI)	PPV (95% CI)	NPV (95% CI)	AUC	Agreement with DMSA*	P-value†
ESR ≥30 mm/h	100.0 (90.17 – 100.0)	97.1 (89.8 – 99.6)	94.7 (82.2 – 99.2)	100.0 (94.5- 100.0)	0.999	0.958	<0.001
CRP ≥1.5 mg/L	100.0 (90.17 – 100.0)	100.0 (94.7 – 100.0)	100.0 (90.17 – 100.0)	100.0 (94.7 – 100.0)	1.000	1.000	<0.001
PCT ≥1 ng/ml	100.0 (90.17 – 100.0)	88.3 (78.1 – 94.8)	81.8 (67.3 – 91.8)	100.0 (93.9 – 100.0)	0.981	0.839	<0.001

Abbreviations: ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; PCT, procalcitonin; CI, confidence interval; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve; DMSA, dimercaptosuccinic acid.
*Kappa coefficient.
†Significance for agreement.

DISCUSSION

In the current study, we found significantly higher ESR, CRP, PCT, and LC in pediatric patients with UUTI compared to those with LUTI. Also, the frequency of positive ESR, CRP, and PCT, as well as leukocytosis was significantly higher in patients with positive DMSA compared to those with negative DMSA. Similarly, Kotoula et al. reported significantly higher CRP, ESR, and PCT in patients with positive DMSA; however, this was not the case for LC in their study.[12] This discrepancy can be due to differences in the demographics of the study populations, the inclusion and exclusion criteria, the accuracy of measurements, and host immune responses. On the other hand, the results of other studies regarding PCT and CRP were in line with our findings.[14-18] Several other studies have also shown significantly higher PCT, CRP, and LC in patients with UUTI compared to those with LUTI.[13,9-22] Contrarily, Tuerlinckx et al. reported no significant difference in terms of PCT, CRP, and LC between patients with negative and positive DMSA. A proportion of their patients had abnormal initial DMSA scans.[23] which shows that it was not their first episode of UTI and this can be the reason behind their findings.

In the current study, PCT ≥1 ng/ml, CRP≥1.5 mg/L, and ESR ≥30 mm/h were 100% sensitive for the early detection of renal parenchymal involvement. Their specificity was 88.3%, 100%, and 97.1%, respectively. Therefore, although CRP and ESR showed better diagnostic performance, PCT also yielded acceptable diagnostic values for the detection of renal parenchymal involvement in pediatric patients with their first episode of UTI. A variety of cut-offs of PCT, CRP, and ESR with different diagnostic values have been proposed by different studies (Table 5). In contrast with our findings, Kotoula et al. demonstrated that PCT was superior to ESR and CRP.[12] Also, Yang et al. reported that although PCT and CRP can both be applied for the differentiation of UUTI from LUTI, PCT has higher sensitivity and specificity for pyelonephritis. They also showed that PCT was significantly correlated with the degree of kidney involvement.[14] Halimi-Asl et al. concluded that serum PCT is a sensitive biomarker for the early detection of acute pyelonephritis; however, negative PCT does not rule out pyelonephritis.[15] In another study, Sheu et al. showed the superiority of PCT to CRP and LC in terms of acute pyelonephritis diagnosis.[19] Chen et al. reported similar results.[20] The variability of diagnostic values in different studies can mostly be explained by the variety of cut-offs; nevertheless, differences regarding the general characteristics of the study populations, especially demographics, inclusion of patients with recurrent UTI in some studies, and the improved accuracy of measurement kits and devices over time can also contribute to these discrepancies. Overall, our results confirmed the acceptable diagnostic performance of PCT ≥1 ng/ml for the detection of UUTI, renal parenchymal involvement, or acute pyelonephritis, reported in previous studies.

One strength of our study was that unlike the majority of previous studies, we evaluated ESR and CRP along with PCT. This way we were able to compare the three biomarkers. Nonetheless, the current study was not without limitations as its relatively small sample size demands cautious generalization of our findings.

Table 5: The proposed cut-offs and diagnostic values of PCT, ESR, and CRP in different studies.

Studies	PCT			CRP			ESR		
	Cut-off*	Sensitivity (%)	Specificity (%)	Cut-off†	Sensitivity (%)	Specificity (%)	Cut-off‡	Sensitivity (%)	Specificity (%)
This study	1	100%	88.3%	1.5	100%	100%	30	100%	97.1%
Kotoula et al.[12]	0.85	89%	97%	3.5	81%	90%	30	85%	73%
Yang et al.[14]	1	90.5%	88%	2	85.7%	48%			
Lucas et al.[16]	0.85	74%	46%						
Halimi-Asl et al.[15]	0.5	83.7%	71.4%						
Sheu et al.[19]	1	81.6%	97.1%	3.5	90.8%	58.3%			
Chen et al.[20]	1.3	86.2%	89.8%						
Nikfar et al.[17]	1	77%	89%	1.5	80%	65%			
Xu et al.[21]	1	87%	76.1%	2.5	70%	82.6%			
Pecile et al.[22]	1	83.3%	93.6%	2	94.4%	31.9%			
Guven et al.[24]	0.96	86.4%	36.4%						
Prat et al.[13]	1	92.3%	61.9%	2	90.6%	34.4%			
Tuerlinckx et al.[23]	1.7	46%	77%	3.4	94%	38.5%			
Zhang et al.[11]	1	84%	91%						
Esteghamati et al.[25]	0.5	30.3%	80%						

Abbreviations: N, number; DMSA, dimercaptosuccinic acid; PCT, procalcitonin; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; LC, leukocyte count.
*Expressed in ng/ml.
†Expressed in mg/L.
‡Expressed in mm/h.

CONCLUSIONS

In the current study, we found that serum PCT ≥1 ng/ml, CRP ≥1.5 mg/L, and ESR ≥30 mm/h are all strong biomarkers for the early detection of renal parenchymal involvement in pediatric UTI. However, the specificity of CRP was higher than PCT and ESR. Altogether, PCT <1 ng/ml can rule out renal parenchymal involvement.

Declarations

Ethics approval and consent to participate

The study received ethics approval from the Ethics Committee of Hormozgan University of Medical Sciences and complies with the statements of the Declaration of Helsinki. Written informed consent was obtained from the parents/guardians of the patients.

Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

Consent for publication

Not applicable.

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Author's contributions

Conceptualization and study validation: KG
Implementation and supervision: KG
Data analysis and interpretation: KG
Writing and reviewing: KG

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