IJKD KIDNEY DISEASES

D-dimer Versus Procalcitonin for the Diagnosis of Pediatric UTI and Prediction of Renal Parenchymal Involvement

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Introduction. Previous studies have investigated the applicability of different serum biomarkers for the diagnosis of urinary tract infection (UTI) and differentiation between acute pyelonephritis (APN) and cystitis. We aimed to compare serum D-dimer with procalcitonin (PCT) for the diagnosis of UTI and prediction of APN in a pediatric population.

Methods. This cross-sectional study included children aged 1 month to 14 years with their first UTI episode confirmed by positive urine culture. Serum PCT and D-dimer were measured in all participants before the initiation of antibiotic therapy. Dimercaptosuccinic acid (DMSA) scan was performed in all children within 2 months of UTI resolution to determine renal parenchymal involvement.

Results. From the 43 children included in this study, 69.8% were female. D-dimer level was significantly higher in boys (823.26 ± 298.19 vs. 582.96 ± 359.96 ng/mL; $P < .05$). PCT level was comparable in boys and girls ($P > .05$). Logistic regression revealed that regardless of gender, children aged 2 to 6 years had significantly higher chance of at least one positive marker compared to those 6 to 14 years (OR = 6.12, 95% CI: 1.09 to 34.47, $P < .05$). The area under the curve value from the receiver operating characteristic curve of D-dimer ≥ 513 ng/mL for prediction of APN was 0.873, with a sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of 84.8, 90, 96.6, 64.3, and 86%; respectively.

Conclusions. According to the results of the current study, 81.4% of children aged 1 month to 14 years with their first UTI episode, were either PCT or D-dimer positive. D-dimer appears to have the highest diagnostic performance for the detection of APN.

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INTRODUCTION

Urinary tract infection (UTI) is one of the most common childhood infections[1] with an incidence of 2.7% in uncircumcised boys and 0.7% in girls during their first year of life.[2] Thereafter, UTI becomes more prevalent in girls compared to boys.[3] When infection only involves the bladder, it is referred to as lower UTI or cystitis, while involvement of the renal parenchyma indicates an upper UTI or acute pyelonephritis (APN).[4] Timely treatment of UTI in children is of considerable importance since renal scarring, occurring in those with APN, is among serious complications and can lead to hypertension in adolescence or early adulthood in approximately 10% of children. Renal insufficiency and end-stage renal disease are other probable consequences of

renal scarring.[5] Therefore, prompt diagnosis and early management of UTIs are essential to prevent such complications.

UTI is primarily diagnosed based on clinical symptoms and the presence of bacteria and white blood cells (WBCs) in urine using dipsticks;[6] nevertheless, this can result in false diagnosis leading to unnecessary administration of empiric antibiotics and subsequent development of antibiotic resistance.[7] Thus, while urine culture is regarded as the gold standard for the diagnosis of UTI,[8] multiple studies have been carried out to evaluate various serum and urine biomarkers in this regard, including C-reactive protein, serum WBC count, leukocyte esterase, procalcitonin (PCT), plasma neutrophil gelatinase-associated lipocalin, immunoglobulin A, xanthine oxidase, lactoferrin, interleukins, heparin-binding protein, myeloperoxidase, and many others.[9,10] However, some of these biomarkers are costly and not readily available for routine testing. More importantly, prediction of renal parenchymal involvement in children with UTI is critical for prevention of further complications. Although dimercaptosuccinic acid (DMSA) scan remains the gold standard for the detection of kidney involvement, both in the setting of APN and for renal scarring as a late sequela of the infection, there are some limitations to the widespread application of DMSA scan, including availability, cost, and exposure to radiation.[11,12]

PCT is a propeptide of calcitonin with long half-life, high specificity, and rapid induction after bacterial stimulation, which has made it a reliable diagnostic biomarker for bacterial infections.[13,14] In fact, it has been reported that serum PCT levels are associated with injury to renal parenchyma.[15,16] A meta-analysis of 18 studies concluded that PCT ≥ 1.0 ng/mL has a high diagnostic performance for the differentiation of acute pyelonephritis from lower UTI.[14]

D-dimer is a fibrin degradation product which represents the activation of the coagulation system.[17] In addition, it is an acute phase reactant which rises in inflammatory conditions and stimulates high levels of cytokines.[18] Yet, very few studies have addressed the correlation between D-dimer levels and infectious or inflammatory diseases.[19]

We aimed to compare serum PCT and D-dimer levels for the diagnosis of UTI and prediction of APN in pediatric patients aged 1 month to 14 years.

MATERIALS AND METHODS

Participants

In this cross-sectional study, children with their first UTI episode, admitted to Bandar Abbas, Children's Hospital from October 22, 2018 to April 20, 2019, were evaluated. Inclusion criteria included age of 1 month to 14 years and positive urine culture ($\geq 10^5$ CFU/mL in bagged specimens, $\geq 10^4$ CFU/mL in catheterized specimens, or $\geq 10^2$ CFU/mL in suprapubic aspirations). Exclusion criteria included any underlying diseases or presence of infection in other organs. All the eligible patients within the above-mentioned period were enrolled in the study.

Study Design

The study received ethics approval code IR.HUMS.REC.1399.009 from the Ethics Committee of Hormozgan University of Medical Sciences and it complies with the statements of the Declaration of Helsinki. After explaining the purpose and providing detailed information about the method of the study, written informed consent was obtained from all the participants' parents or guardians. Demographic features including age and gender were recorded for each patient. All patients were visited and examined by a pediatric nephrologist. Urinalysis and urine culture were performed for all participants and those with a positive urine culture were included. The number of WBCs per high-power field (HPF) was determined in urine sediment. Body temperature was measured using a standard tympanic thermometer and fever was defined as > 38 °C in children < 3 years, > 37.8 °C in children 3 to 11 years, and > 37.6 °C in children > 11 years. Accordingly, all children in the study were febrile. Before the initiation of antibiotics, two separate one-milliliter venous blood samples were collected from each participant. D-dimer was measured quantitatively in one of the samples using latex enhanced immunoturbidometric assay (Sclavo D-Dimer Kit, Sclavo Diagnostics International, Italy) with Mindray—BS-800M Clinical Chemistry Analyzer (Shenzhen Mindray Bio-Medical Electronics Co., Ltd, China). PCT was measured semi-quantitatively in the other sample using one-step immunochromatographic assay (B.R.A.G.M.S PCT-Q, Germany). D-dimer ≥ 500 ng/mL and PCT ≥ 0.5 ng/mL were considered positive. Dimercaptosuccinic acid (DMSA) scan was performed on all children within 2 months using

Siemens E.Cam® single-head scanner. Scans with poor uptake in renal parenchyma were regarded as positive. The results were used as reference for determination of optimal PCT and D-dimer cut-offs in the diagnosis of upper UTI.

Data Analysis

The Statistical Package for the Social Sciences (SPSS) software (version 25.0, Armonk, NY: IBM Corp. USA) was used for data analysis. Mean, standard deviation, frequency, and percentages were used to describe the results. Fisher's exact test was used to compare qualitative data. Due to the abnormal distribution of quantitative variables (based on Kolmogorov-Smirnov normality test), Kruskal-Wallis and Mann-Whitney tests were used for comparisons and Spearman's Rho for correlation. Binary logistic regression was used to determine the odds ratio (OR). *P* values ≤ .05 were considered as statistically significant. Area under the curve (AUC) values from the receiver operating characteristic (ROC) curves of D-dimer and PCT were used for prediction of APN and determination of the optimal cut-off value for each. Taking the optimal cut-off into account, sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and diagnostic accuracy of both D-dimer and PCT were calculated.

RESULTS

From the 43 children included in this study, 13 (30.2%) were male and 30 (69.8%) were female. Their mean age was 3.53 ± 3.76 years (range: 4 months to 12 years). No significant difference was found in age between boys and girls (2.81 ± 3.46 vs. 3.85 ± 3.89 years, $P > .05$). Mean urine WBC was 14.93 ± 6.48 per HPF (range: 7 to 29). Mean PCT and mean D-dimer were 0.58 ± 0.87 and 655.61 ± 356.85 ng/mL, respectively. *E. coli* was the most common bacterium isolated from urine cultures (65.1% [28/43]). In general, positive PCT was observed in 12 (27.9%) and positive D-dimer

Table 1. General Characteristics of the Study Population

Variable	n (%)
Gender	
Male	13 (30.2)
Female	30 (69.8)
Age	
1 month to 2 years	25 (58.1)
2 to 6 years	7 (16.3)
6 to 14 years	11 (25.6)
Isolated Bacteria	
E. coli	28 (65.1)
Klebsiella	6 (14.0)
Enterococcus	3 (7.0)
Proteus	5 (11.6)
S. Saprophyticus	1 (2.3)
PCT	
Positive	12 (27.9)
Negative	31 (72.1)
D-dimer	
Positive	30 (69.8)
Negative	13 (30.2)

Abbreviations: n, number; PCT, procalcitonin; *E. coli, Escherichia coli*; *S. saprophyticus, Staphylococcus saprophyticus*.

Table 2. The Association of PCT with Gender, Age, and Type of Bacteria Isolated from Culture

Variables	PCT (ng/mL)	*P*	PCT (n (%))		*P*‡
	Mean ± SD		Positive	Negative	
Gender					
Male	0.72 ± 1.03	> .05*	4 (30.8)	9 (69.2)	> .05
Female	0.53 ± 0.81		8 (26.7)	22 (73.3)	
Age					
1 month to 2 years	0.61 ± 0.99	> .05†	6 (24.0)	19 (76.0)	> .05
2 to 6 years	0.61 ± 0.63		3 (42.9)	4 (57.1)	
6 to 14 years	0.50 ± 0.75		3 (27.3)	8 (72.7)	
Bacteria					
E. coli	0.68 ± 1.01	> .05†	8 (28.6)	20 (71.4)	> .05
Klebsiella	0.32 ± 0.35		1 (16.7)	5 (83.3)	
Enterococcus	0.32 ± 0.31		1 (33.3)	2 (66.7)	
Proteus	0.63 ± 0.81		2 (40.0)	3 (60.0)	
S. saprophyticus	0.12 ± 0.00		0 (0.0)	1 (100.0)	

Abbreviations: SD, standard deviation; n, number; PCT, procalcitonin; *E. coli, Escherichia coli*; *S. saprophyticus, Staphylococcus saprophyticus*.
*Analyzed by Mann-Whitney test.
†Analyzed by Kruskal-Wallis test.
‡Analyzed by Fisher's exact test.

in 30 (69.8%) (Table 1). Both PCT and D-dimer were positive in 16.3% (7/43) and 81.4% (35/43) of the patients had at least one positive marker.

Mean PCT did not differ significantly by gender, age, and type of bacteria isolated from urine culture ($P > .05$). Positive PCT was higher in boys, age 2 to 6 years, and cultures positive for *Proteus*, with no statistically significant difference ($P > .05$) (Table 2).

Mean D-dimer was significantly higher in boys compared to girls (823.26 ± 298.19 vs. 582.96 ± 359.96 ng/mL, $P < .05$). However, there was no difference in mean D-dimer by age and type of bacteria isolated from urine culture ($P > .05$). Positive D-dimer was higher in boys, age 2 to 6 years, and cultures positive for *Klebsiella* ($P > .05$) (Table 3).

Only one culture specimen was positive for *S. saprophyticus*, with positive corresponding D-dimer and negative PCT. There was no significant correlation between D-dimer and PCT results (r = -0.087, $P > .05$).

Binary logistic regression revealed that the odds of having at least one positive marker (PCT or D-dimer) was significantly higher in children aged 2 to 6 years compared to those aged 6-14 years (OR = 6.11, 95% CI: 1.13 to 33.19; $P < .05$). This association remained significant after adjustment for gender (OR = 6.12, 95% CI: 1.09 to 34.47, $P < .05$). Besides, every additional WBC per HPF significantly increased the odds of simultaneous positivity of both PCT and D-dimer (OR = 1.16, 95% CI: 1.01 to 1.32, $P < .05$) even after gender adjustment (OR = 1.20, 95% CI: 1.02 to 1.41, $P < .05$).

ROC curves for the prediction of APN are shown in Figure. Table 4 shows that highest AUC from the ROC curve for prediction of APN belongs to D-dimer with the optimal cut-off of 513 ng/mL. The highest sensitivity belongs to having at least one positive test (based on previous cut-offs), while the highest specificity and PPV are seen with having positive results in both tests. D-dimer ≥ 513 ng/mL and having at least one positive test showed identical and the highest diagnostic accuracy.

Table 3. The Association of D-dimer with Gender, Age, and Type of Bacteria Isolated from Culture

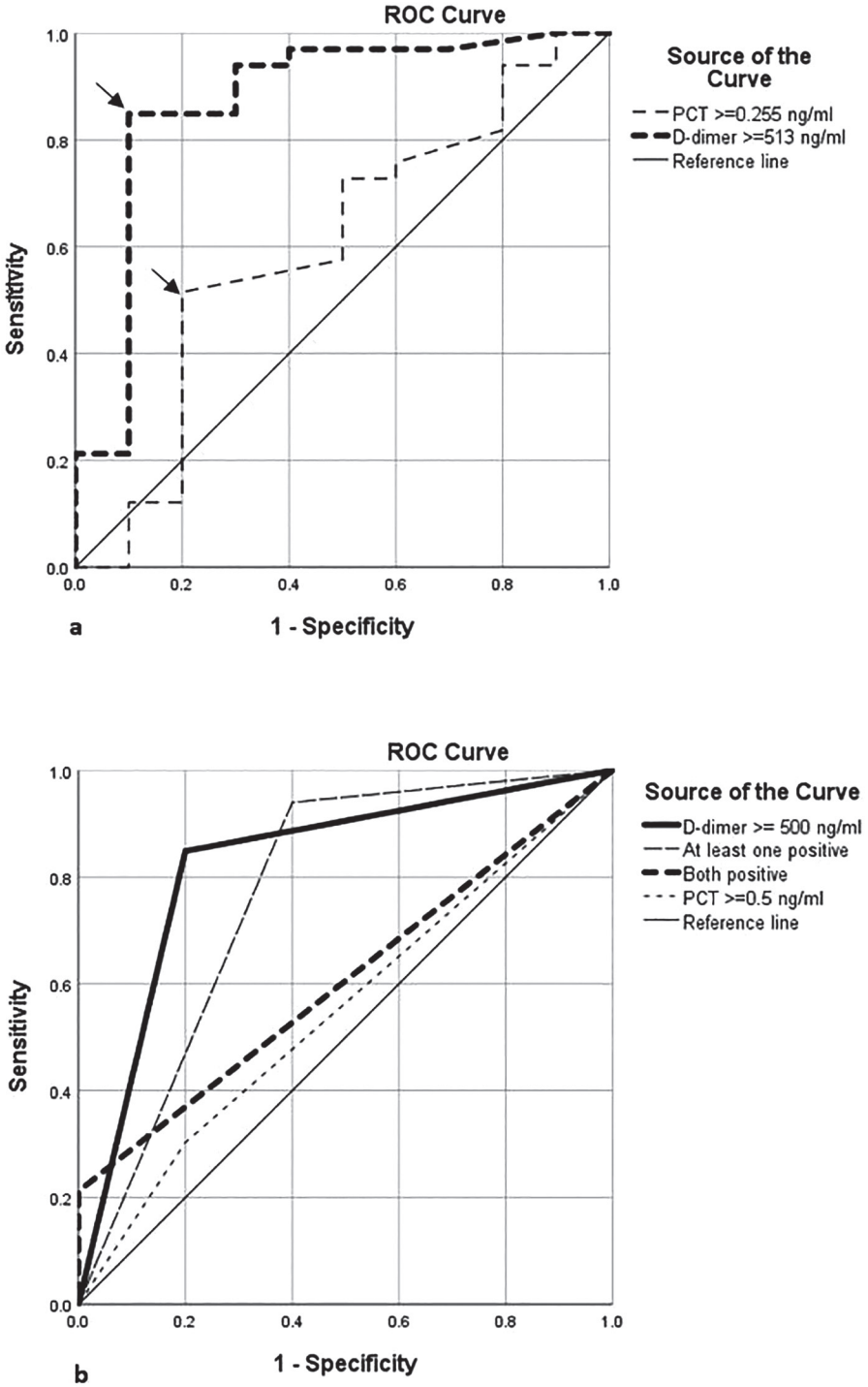
Variables	D-dimer (ng/mL)	*P*	D-dimer (n (%))		*P*‡
	Mean ± SD		Positive	Negative	
Gender					
Male	823.26 ± 298.19	> .05*	11 (84.6)	2 (15.4)	> .05
Female	582.96 ± 359.96		19 (63.3)	11 (36.7)	
Age					
1 month to 2 years	627.85 ± 306.65		18 (72.0)	7 (28.0)	
2 to 6 years	793.65 ± 416.55	> .05†	6 (85.7)	1 (14.3)	> .05
6 to 14 years	630.85 ± 434.85		6 (54.5)	5 (45.5)	
Bacteria					
E. coli	709.94 ± 394.30		21 (75.0)	7 (25.0)	
Klebsiella	646.11 ± 342.79		5 (83.3)	1 (16.7)	
Enterococcus	521.92 ± 170.69	> .05†	1 (33.3)	2 (66.7)	> .05
Proteus	473.49 ± 211.37		2 (40.0)	3 (60.0)	
S. saprophyticus	503.00 ± 0.00		1 (100.0)	0 (0.0)	

Abbreviations: SD, standard deviation; n, number; *E. coli, Escherichia coli*; *S. saprophyticus, Staphylococcus saprophyticus*.
*Analyzed by Mann-Whitney test.
†Analyzed by Kruskal-Wallis test.
‡Analyzed by Fisher's exact test.

Table 4. Diagnostic Performance for Detection of Upper UTI

Cut-off	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)	Diagnostic Accuracy (%)	AUC
D-dimer ≥ 513 ng/mL	84.8	90.0	96.6	64.3	86.0	0.873
D-dimer ≥ 500 ng/mL	84.8	80.0	93.3	64.5	83.7	0.824
PCT ≥ 0.255 ng/mL	51.5	80.0	89.5	33.3	58.1	0.600
PCT ≥ 0.5 ng/mL	30.3	80.0	83.3	25.8	41.9	0.552
At Least 1 Positive*	93.9	60.0	88.6	75.0	86.0	0.770
Both Positive*	21.2	100.0	100.0	27.8	39.5	0.606

Abbreviations: PCT, procalcitonin; PPV, positive predictive value; NPV, negative predictive value; AUC, area under the curve.
*PCT ≥ 500 ng/mL, D-dimer ≥ 0.5 ng/mL



Receiver operating characteristic (ROC) curves for the prediction of APN (a) D-dimer ≥ 513 ng/mL, PCT ≥ 0.255 ng/mL, and (b) D-dimer ≥ 500 ng/mL, PCT ≥ 0.5 ng/mL, at least one positive test, and both positive.

DISCUSSION

Despite urine culture being the gold standard for the diagnosis of UTI,[8] it is time-consuming and can yield contamination. Pediatric patients require a more rapid method for confirmation of the UTI diagnosis because any delay in treatment can result in potentially irreversible complications, and on the other on the other hand, administration of empiric antibiotics in children without definite UTI may lead to unnecessary antibiotic resistance.

Furthermore, urine nitrite, leukocyte esterase, and WBC count (pyuria) are indicators of UTI in urinalysis, the most common test performed in patients with suspected UTI. Yet, nitrite lacks sufficient sensitivity and negative predictive value, and neither leukocyte esterase nor leukocyte count have acceptable specificity for UTI.[9,20,21]

In the current study, we found that in children with a first UTI episode, D-dimer positivity rate was 2.5-fold higher than PCT. In addition, boys had significantly higher D-dimer levels compared to girls, while PCT did not differ considerably across genders. We also found higher odds of having at least one positive marker (PCT or D-dimer) in children aged 2 to 6 years compared to those aged 6 to 14 years, irrespective. However, age was not a predictive factor for the positivity of any of these tests alone. In the same way, the type of bacteria isolated from urine culture did not influence PCT or D-dimer results. Although 84.1% of children with culture-confirmed UTI had tested positive for at least one marker, in many settings, both tests could not be performed or may not be available, especially in developing countries. Therefore, according to the findings of the current study, in such conditions of limited resources, D-dimer is preferred for the diagnosis of UTI in pediatric patients due to its lower false negative rates.

PCT is a precursor of calcitonin, primarily a thyroid hormone, with negligible blood levels under normal circumstances which rises in the presence of bacterial infections.[22] It has also been demonstrated that PCT can strongly predict UTI severity.[23,24] The role of PCT in differentiating acute pyelonephritis from lower UTI has been investigated in previous studies; however, its utility in the diagnosis of UTI (lower or upper) has rarely been addressed. Levine *et al.* showed that PCT < 0.25 ng/mL can rule out UTI; nevertheless, values higher than this threshold were poor predictors of positive UTI diagnosis. Moreover, their study was performed on adults and the same cut-off may not be applicable to children.[25] Similarly, Drozdov *et al.* suggested the same cut-off for PCT, below which antibiotics for UTI should be discontinued or withheld.[26] In our study, for qualitative assessment of PCT we regarded PCT ≥ 0.5 ng/mL as positive, which is higher than the above-mentioned threshold. We solely evaluated children who had positive urine cultures; whereas, for the determination of an appropriate PCT cut-off to predict UTI or lack of UTI, a number of children with suspected UTI but negative cultures should also be included. Thus, we were unable to establish a PCT cut-off for the diagnosis of UTI in children based on the findings of the current study. Likewise, the same is warranted for specifically assigning a D-dimer cut-off in pediatric UTI.

Since D-dimer is the final product of fibrin degradation and mirrors the activation of the coagulation cascade, its levels can increase in conditions involving thrombosis, such as venous thromboembolism, disseminated intravascular coagulation, infection, inflammation, and even stroke or ischemic heart disease.[17,27] Indeed, D-dimer has long been a part of the criteria for the diagnosis of pulmonary thromboembolism.[28] Nonetheless, only one previous study has reported its significance as an inflammatory marker of UTI.[19] In this study by Lee *et al.*, D-dimer was superior to other markers including serum WBC count and erythrocyte sedimentation rate (ESR), but was inferior to C-reactive protein (CRP) in predicting upper UTI.[19] D-dimer has also been proposed as a strong prognostic factor in patients with suspected infection or sepsis.[29]

With 100% specificity and 90% sensitivity, DMSA scan is currently the gold standard for the detection of renal parenchymal involvement.[30,31] However, due to some limitations, it cannot be routinely used in clinical practice. We performed a DMSA scan in all the children of our study. Taking the results of DMSA as reference, we found that D-dimer ≥ 513 ng/mL was 84.8% sensitive and 90% specific for differentiating upper from lower UTI. The corresponding diagnostic values were 51.5% and 80% for PCT ≥ 0.255 ng/mL; respectively. In comparison with the default cut-offs for D-dimer and PCT, AUC value from the ROC of D-dimer ≥ 513 ng/mL was the highest for prediction of APN. Interestingly, altogether, the diagnostic in our study was even better than what Zhang *et al.* reported in their meta-analysis on PCT. They found a pooled sensitivity of 86% and a pooled specificity of 76% for PCT for the diagnosis of APN.[32]

As mentioned earlier, the only research that had investigated D-dimer as a marker of APN demonstrated the superiority of this marker over ESR and serum WBC count, and its inferiority to

CRP for the prediction of APN. Lee *et al.* reported an AUC of 0.643 for D-dimer for the detection of upper UTI and 428 ng/mL was proposed as the best cut-off.[19] Their sample size was larger than ours. Moreover, only infants younger than 24 months were evaluated in this study which can explain the discrepancy between their findings and ours. Besides, since they did not measure PCT, no comparison was made between this marker and D-dimer.

The primary strength of our study was that it was the first research to compare D-dimer with PCT for the detection of APN. In addition, the D-dimer cut-off that we established introduces this marker as an appropriate test to predict APN and guide treatment regimens, especially in the setting of limited resources. On the other hand, a major limitation to our study was the small sample size, which calls on cautious interpretation and generalization of the results.

CONCLUSION

The results of the current study demonstrated that D-dimer and PCT were both positive in only 16.3% of children aged 1 month to 14 years with their first UTI episode. Although performing both tests would increase the probability of UTI detection in this population because 81.4% of children had at least one positive test, the frequency of positive D-dimer was approximately 2.5 times the frequency of positive PCT, which makes D-dimer a more appropriate test for the diagnosis of pediatric UTI with a lower false negative rate. Besides, D-dimer was superior to PCT for the detection of. Further studies are required to confirm the findings of the current study.

ABBREVIATIONS

- APN: Acute Pyelonephritis
- AUC: Area Under the Curve
- CFU: Colony Formation Unit
- DMSA: Dimercaptosuccinic Acid
- HPF: High-power Field
- *S. Saprophyticus: Staphylococcus Saprophyticus*

DECLARATIONS

Ethics Approval and Consent to Participate

The study received ethics approval from the Ethics Committee of Hormozgan University of Medical Sciences under the ethics code: IR.HUMS.REC.1399.009 and it complies with the statements of the Declaration of Helsinki.

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.

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Author's Contributions

Conceptualization and study validation: ME
Implementation and supervision: MZ
Data analysis and interpretation: HD
Writing and reviewing: KG and GZ

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