

Diagnostic Accuracy of the Quantitative C-Reactive Protein, Erythrocyte Sedimentation Rate and White Blood Cell Count in Urinary Tract Infections among Infants and Children

Parviz AYAZI¹, Abolfazl MAHYAR¹, Mohammad Mahdi DANESHI¹, Hassan JAHANI HASHEMI¹, Mahdieh PIROUZI¹, Neda ESMAILZADEHHA²

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¹ Qazvin University of Medical Sciences, Children Hospital, Shahid Beheshti Blvd, Po Box 3415914595, Qazvin, Iran

² Metabolic Diseases Research Center, Qazvin University of Medical Sciences, Booali-Sina Hospital, Booali-Sina Street, Po Box 3413786165, Qazvin, Iran

Abstract

Objectives: The aim of this study was to evaluate the diagnostic accuracy of the quantitative C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and white blood cell (WBC) count in urinary tract infections (UTI) among hospitalised infants and children in Qazvin, Iran.

Methods: This cross-sectional study was conducted on 127 hospitalised children ranging in age from 2 months to 12 years old 31.79 months (SD 30.73) who were suspected of having a UTI and who did not receive antibiotics prior to being seen at a Qazvin teaching children's hospital between 2005 and 2006. A urine analysis (U/A) and urine culture (U/C) were performed. The blood was taken for CRP, ESR and WBC analyses. U/C has been considered the gold standard test for a UTI and dimercaptosuccinic acid renal scintigraphy (DMSA) as the gold standard for an upper UTI (pyelonephritis). These tests were used to determine the diagnostic accuracy, which is represented as the percent of correct results.

Results: Within the study population, 72 patients (56.7%) were younger than two years old 9.86 months (SD 4.56) and 55 (43.3%) were older than two years old 63.58 months (SD 30.96). One hundred and two patients (80.3%) were female. There were 100 cases that had a positive U/C. Of the patients with a positive U/C, 81 had pyuria (WBC more than 5/hpf), 71 had a peripheral WBC count of more than 10 000 /mL, 95 had a CRP of more than 10 mg/L and 82 had an ESR > 10 mm/h. The sensitivity and specificity as well as the positive and negative predictive values and the accuracy of CRP when using U/C as the gold standard were, respectively, 96%, 11.1%, 80.2%, 50%, and 78%; when using ESR as the gold standard were, respectively, 55%, 40%, 77.6%, 17.2%, and 52%; and when using WBC counts as the gold standard were, respectively, 69%, 52%, 86.6%, 35.6%, and 65%. The accuracy of CRP, ESR and WBC counts when considering the DMSA as the gold standard were 58.3%, 62.8%, and 64.5%, respectively.

Conclusion: Although acute phase reactants can help in the diagnosis of a UTI, they are not pathognomonic. CRP, ESR and WBC were neither completely sensitive nor specific for detecting a UTI and its localisation site in Iranian children. Therefore, in a country where advanced clinical diagnostic tests are available, the advanced test should be used in conjunction with CRP, ESR and WBC analyses. Finally, a combination of laboratory tests along with history and exact clinical examination are needed for the diagnosis of a UTI and its localisation site.

Keywords: children, DMSA renal scintigraphy, erythrocyte sedimentation rate, Urinary tract infection, quantitative C-reactive protein

Introduction

Urinary tract infections (UTI) are a common problem in infants and children, with a prevalence of 6.5% and 3.3% in girls and boys younger than one year of age, respectively (1). In childhood, UTIs are 2- to 4-fold more prevalent in girls than

in boys, and 5% of school girls contract a UTI during their school years. Although the prevalence rate of UTIs is affected by age, gender, race, and circumcision status, the highest prevalence of UTI occurs in uncircumcised males younger than three

months of age and in females less than 12 months of age. In another study, the overall prevalence of UTI was 7% in infants, with a chief complaint of fever (1,2).

The presumptive diagnosis of a UTI in children is often based on the results of a microscopic urine analysis (U/A). Most infections remain undiagnosed if tests are not routinely performed to detect them (3). The most frequent pathogen is *Escherichia coli*, accounting for approximately 85% of UTIs in children (4). Common uropathogens consist of *Escherichia coli* (accounting for approximately 85% of UTIs in children), *Klebsiella*, *Proteus*, *Enterobacter*, *Citrobacter*, *Staphylococcus saprophyticus* and *Enterococcus* (4). The general route of infection in the urinary tract is ascending, and the pathogens originate from the perineal flora (1).

Renal parenchymal defects occur in 5–15% of children within one to two years of their first presentation with a UTI and is associated with an increased risks of progressive renal damage. The risk of parenchymal defects most likely diminishes over time (5). In some studies, renal scarring was present in 8–40% of patients following an event of acute pyelonephritis. As a consequence of the renal scars, patients had increased hypertension and variable degrees of renal failure. The discrimination among upper and lower UTIs has significant medical implications in children younger than two years of age. In this group, the clinical presentation tends to be non-specific, and the possibility of renal damage after acute pyelonephritis is considered to be higher than in older children (6).

The aim of this study was to evaluate the diagnostic accuracy of the quantitative C-reactive protein (CRP), erythrocyte sedimentation rate (ESR) and peripheral white blood cell (WBC) count in UTIs among hospitalised infants and children in Qazvin, Iran.

Materials and Methods

In this cross-sectional study, we assessed 127 child patients admitted at the teaching children's hospital of Qazvin, which is affiliated with the Qazvin University of Medical Sciences, who were suspected of having a UTI based on clinical findings and an active U/A between 2005 and 2006. The study was approved by the Hospital Ethical committee, and consent forms were obtained from the children's parents.

Children who had received an antibiotic agent within the previous week were excluded. Children with known concomitant diseases, any

type of renal disorder or a previous diagnosis of vesicoureteral reflux were excluded. Every child underwent a history and physical examination, and a full evaluation for UTI was performed.

All of the urine samples were obtained by a clean void midstream catch, by suprapubic aspiration or by sterile collection bags and were sent for culturing less than 1 hour after collection. The bladder tap was performed after the infant had been well hydrated intravenously or 1 hour after feeding. All of the U/A were performed in the clinical laboratory of the Qazvin Children's hospital. The specimens were analysed by a standard U/A. For the standard U/A, specimens were centrifuged at 2000 rpm for 10 minutes and were examined microscopically for pyuria, which is reported as the number of leukocytes per high-power field (HPF). For a standard U/A, pyuria was defined as > 5 WBCs/HPF.

A loop calibrated to deliver 0.01 mL of urine was used to inoculate plates containing sheep blood agar and MacConkey agar. All of the plates were inoculated at 35–37 °C and examined at 24 to 48 hours after culturing to determine a colony count as well as bacterial identification. UTI was defined as a single organism $\geq 10^5$ CFU/mL in the urine culture or the combination of a colony count $\geq 10^4$ CFU/mL and a symptomatic child (4). Upon admission, the WBC count, plasma CRP and ESR values were determined in all of the children. CRP was measured in ethylenediaminetetraacetic acid (EDTA)-blood samples by a rapid immunometric method (quantitative test kit for CRP, Parsazmun Co., Tehran, Iran).

According to the manufacturer's instructions, values of 10 mg/L were considered abnormal. The ESR was measured in EDTA-Blood samples by the Wintergreen method. For measuring the ESR, we mixed one volume of 109 mmol/L (32 g/L) trisodium citrate with four volumes of blood before performing the test. The mixed samples were added to a Westergren tube (Siemens Co., Munich, Germany) up to the 200 mm mark with a pipette. We placed the tubes in a vertical position and left them undisturbed for 60 minutes free from vibration, draughts and direct sunlight; then, we measured the height of the clear plasma above the upper limit of the column of sedimenting cells. The results were expressed as ESR=X mm in one hour.

To localise the site of UTI, we used a dimercaptosuccinic acid renal scintigraphy (DMSA) scan as the gold standard for the diagnosis of acute pyelonephritis (7). In addition to acute phase reactants, the serum sodium concentration was used to assess the severity of the damage to

the renal tissue (8).

Statistical Analysis

The diagnostic accuracy was defined as (True Positive + True Negative)/Total. Sensitivity and specificity as well as positive and negative predictive values were calculated based on the increased ESR and CRP concentrations in the serum of the patients with a positive U/C; this was used as the validating standard for UTI. The results were reported as frequencies and percentages as well as the mean ± standard deviation (SD). The independent *t* test or the Mann-Whitney U test were used where appropriate. A *P* value < 0.05 was considered significant. All of the analyses were performed using the SPSS software, version 19.

Results

This cross-sectional study included 127 children and infants up to 12 years of age. Only 96 patients were enrolled for the statistical analysis, and four patients with a positive urine culture did not wish to continue the study. The

ages of the patients ranged from 2 months to 12 years; 31.79 (SD 30.73). Out of 127 patients, 72 patients (56.7%) were < 2 years of age 9.86 months (SD 4.56) and 55 patients (43.3%) were more than 2 years old 63.58 months (SD 30.96).

Among 127 patients with a UTI, 102 patients (80.3%) were female and 25 patients (19.7%) were male. Of 96 patients with a positive U/C, 54 patients had a positive DMSA renal scintigraphy and 42 patients had a negative DMSA renal scintigraphy. The characteristics of the subjects and their age distribution with regards to the DMSA results are shown in Tables 1 and 2.

The most frequent signs and symptoms were fever (70.1%), dysuria (36.2%), vomiting (28.3%), diarrhoea (22%), malodorous urine (22%), abdominal or flank pain (18.9%), poor feeding (16.5%) and urinary frequency (12.6%). Of the 127 patients suspected of having a UTI, 100 patients (79%) had a positive U/C and 27 patients (21%) had a negative U/C. Of the 96 children with a definitive diagnosis of a UTI (positive U/C), 71 were febrile, 81 had pyuria > 5 WBC/Hpf, 71 had a peripheral WBC > 10 000

Table 1: Characteristics of the subjects

	Whole population	children with Cystitis	children with Pyelonephritis	<i>P</i> value ^e
Age (month)	33.13 (33.71) ^f	27.07 (27.34)	35.46 (32.92)	0.186 ^g
CRP ^a (mg/L)	33.20 (18.47)	30.52 (16.49)	39.24 (20.21)	0.026 ^g
ESR ^b (mm/h)	24.79 (27.77)	16.48 (19.18)	35.35 (33.08)	0.001 ^g
WBC ^c count (per mm ³)	12629 (5070)	11990 (5375)	14290 (4642)	0.027 ^h
Granulocyte (%)	54.06 (18.91)	51.24 (20.35)	58.83 (18.53)	0.059 ^h
WBC in U/A ^d	41.65 (40.55)	36.36 (39.71)	52.33 (42.85)	0.062 ^g

^a C-reactive protein; ^b Erythrocyte sedimentation rate; ^c White blood cell count; ^d urine analysis; ^e between children with cystitis and children with pyelonephritis; ^f Mean (SD); ^g *P* value by Mann Whitney U test; ^h *P* value by *t* test.

Table 2: Demographics of 96 patients with positive urine culture

DMSA Age	DMSA ^a Positive		DMSA Negative	
	Male	Female	Male	Female
0 – 2 months	0	1 (1.04) ^b	0	0
2 – 12 months	4 (4.16)	18 (18.75)	4 (4.16)	17 (17.70)
12 – 24 months	1 (1.04)	6 (6.25)	2 (2.08)	3 (3.125)
24 months – 12 years	3 (3.125)	21 (21.87)	5 (5.20)	11 (11.45)
Total	8 (8.33)	46 (47.91)	11 (11.45)	31 (32.29)

^a Dimercaptosuccinic acid renal scintigraphy.

^b Number (percent).

mL, 95 had a CRP > 10 mg/L and 82 had an ESR > 10 mm/h.

The sensitivity, specificity, and accuracy of the quantitative CRP, ESR, peripheral WBC count and granulocyte using DMSA renal scintigraphy as the gold standard for pyelonephritis is shown in Table 3. The sensitivity and specificity as well as the positive and negative predictive value and accuracy of quantitative CRP were 96%, 11.1%, 80.2%, 50%, and 78%, respectively; of ESR were 55%, 40%, 77.6%, 17.2%, and 52%, respectively; and of WBC were 69%, 52%, 86.6%, 35.6%, 65%, respectively, when using U/C as the gold standard (Table 4).

Discussion

The distinction between a lower and upper UTI is important because renal involvement can induce parenchymal scarring that may lead to arterial hypertension and chronic renal failure (1). In addition, the rapid diagnosis of pyelonephritis results in proper treatment and reduces renal scarring (9). Previous studies noted that even children with unilateral renal disease are at risk for long-term complications (10). Therefore,

the rapid diagnosis of acute pyelonephritis is significant because early aggressive treatment reduces the risk of renal scarring (11).

In this study, we used a sensitive technique to assess the involvement of renal parenchymal. It is known that DMSA renal scintigraphy performed during the acute phase of infection is sensitive for assessing the involvement of renal parenchymal; in addition, DMSA is known as the gold standard for the diagnosis of acute pyelonephritis (11). Any area of reduced or devoid radioactivity in the renal cortex was considered a positive result. However, DMSA renal scintigraphy is expensive, not available in all centres and exposes the patients to radiation. Moreover, some believe that it may not differentiate old scarring from acute renal involvement unless a follow-up scanning is performed (11). Some believe that there is photopenia in acute pyelonephritis but that the size of kidney is preserved. In addition, the size of the kidney may increase due to inflammation. Finally, in acute pyelonephritis, the border of the kidney is completely preserved. However, with old scarring in the presence of reduced uptake, there is volume loss, and a wedge shape appearance in the cortex of kidney.

Table 3: Sensitivity, specificity and accuracy of laboratory data in diagnosis of acute pyelonephritis

	Sensitivity ^g	Specificity ^g	Accuracy ^g	PPV ^{d,g}	NPV ^{e,g}	LR ^f (+)	LR (-)
CRP ^a (> 10 mg/L)	98.1	7.1	58.3	57.6	75	1.05	0.27
ESR ^b (> 10 mm/h)	70.4	52.5	62.8	66.7	56.7	1.48	0.56
WBC ^c count (> 10000 /mm ³)	81.5	42.9	64.5	64.7	64.3	1.42	0.43
Granulocyte (> 50%)	53.7	61.9	57.3	64.4	51	1.41	0.75

^a C-reactive protein; ^b Erythrocyte sedimentation rate; ^c White blood cell count; ^d Positive Predictive Value; ^e Negative Predictive Value; ^f Likelihood Ratio; ^g Data are presented as percent; The cut-off value used for each parameter is reported in parentheses. DMSA renal scintigraphy as gold standard.

Table 4: Comparison of the results of diagnostic tests in relation to positive urine culture

	Standard UA ₅ WBC HPF	Granulocyte > 50%	ESR > 10 mm/h	Peripheral WBC > 10000 mm	CRP > 10 mg/L	qualitative CRP
Sensitivity ^a	76	40	55	69	96	53
Specificity ^a	4	51.9	40	52	11.1	69
Accuracy ^a	61	42.5	52	65	78	56
PPV ^{a,b}	75.2	75.5	78.6	84.1	80	86.2
NPV ^{a,c}	4	18.9	18.2	31.1	42.9	28.6
LR ^d (+)	0.79	0.83	0.92	1.44	1.1	1.71
LR (-)	6	1.16	1.125	0.6	0.4	0.68

^a Data are presented as percent; ^b Positive Predictive Value; ^c Negative Predictive Value; ^d Likelihood Ratio. Urine culture as gold standard.

Considering the relative limitations of DMSA renal scintigraphy, we attempted to assess the significance of acute phase reactants (ESR, CRP, and WBC) in patients with acute pyelonephritis compared with those with acute cystitis. We attempted to locate a blood marker that could correlate with the DMSA renal scan.

CRP, ESR and peripheral WBC count are simple noninvasive tests that are used for the diagnosis of invasive bacterial infections and for determining the UTI level. Some studies have shown a statistically significant increased level of WBC, CRP and ESR in patients with acute pyelonephritis compared with those with acute cystitis. On the other hand, there are studies that do not emphasise the significance of haematological factors in discriminating upper from lower UTIs (12–15).

In children with pyelonephritis, the mean CRP value 39.24 (SD 20.21) (Table 2) was higher than in children with cystitis 30.52 (SD 16.49), which is consistent with the study performed by Alberto, Biggi, et al.(12). The other biological parameters, such as ESR ($P < 0.001$) and WBC per mm³ ($P < 0.027$), were helpful in differentiating those with and without kidney involvement.

However, 1 out of 54 children (1.8%) with pyelonephritis had a CRP level below the cut-off value (false negative patients regarding positive DMSA renal scintigraphy), and 42 (43%) children with cystitis had a CRP level above the cut-off value (false positive patients regarding negative DMSA renal scintigraphy).

From these results, we calculated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and accuracy of CRP (98.1%, 7.1%, 57.6%, 75% and 58.3%, respectively); the DMSA renal scan was considered to be the gold standard. The median CRP level of our study was 28, which is in accordance with the study by Jakobsson (16). The median CRP level of our study with a normal DMSA scan was lower compared to those with an abnormal scan (27 mg/dL vs 36.5 mg/dL), which is in accordance with Jakobsson's study (15 mg/dL vs 98 mg/dL).

In our study, CRP was elevated in 55% of patients with an abnormal DMSA renal scintigraphy and in 40% of patients with a normal scan. Melis et al. found an elevated CRP level in 57% of patients with an abnormal DMSA renal scintigraphy and in 33% of patients with a normal scan (17).

In our study, we found that an elevated CRP level (> 10 mg/dL) had a 98.1% (Table 2)

sensitivity and 7.1% specificity in identifying a renal lesion, but Benador found a sensitivity of 89% and specificity of 25% (18). In another study by Eduardo H. Garin, the sensitivity, specificity and accuracy of CRP were 100%, 8% and 48%, respectively (6).

In our study, the WBC values are able to identify kidney involvement, with a sensitivity of 81.5%, but the specificity of WBC was 42.9%, which is in accordance with the study of Biggi (77% and 18%, respectively) (12) and a study by Grain (89% and 27%, respectively) (6). In our study, the sensitivity, specificity and accuracy of ESR were, respectively, 70.37%, 53% and 62.8%, but in the study performed by Garin, these values were 100%, 8% and 62%, respectively. The study of Alberto Biggi showed a different sensitivity, specificity and accuracy, which were 48%, 50% and 59%, respectively (12).

The sensitivity, specificity and accuracy of pyuria (> 5 WBC/HPF) in our study for diagnosing renal lesions were 81.5%, 28.6% and 58.3%, respectively. However, the study of Garin showed a sensitivity, specificity and accuracy of pyuria of 82%, 28% and 51%, respectively, and the research of Dar-Shong Lin showed values of 59%, 93% and 88%, respectively (3). In other studies, an increased ESR and differential leukocyte count were in favour of pyelonephritis and were helpful in localising the site of the UTI. In contrast, CRP was not able to localise the site of the UTI (19,20). In the present study, CRP and ESR were neither completely sensitive nor specific for the localisation site of UTI.

In another study, the mean WBCs were significantly higher in patients with acute pyelonephritis compared to patients with a lower UTI ($P < 0.01$) (15). In the present study, the WBCs were significantly higher in patients with acute pyelonephritis than in patients with cystitis ($P < .027$), which is in accordance with a previous study (Table 2). In a study by Ahmed J Al-Sayyad, the sensitivity and specificity of CRP for the prediction of acute pyelonephritis were 95.9% and 88.2%, respectively. On the other hand, the sensitivity and specificity of CRP in the present study were 98.1% and 7.1%, respectively. The sensitivities of CRP in the two recent studies are similar, while the sensitivity is remarkably lower in the present study. This difference could be due to many factors, such as age and sex differences in the populations studied, the techniques used to identify UTIs, laboratory kit, nutrition, race and so on.

The diagnosis of acute pyelonephritis is

important for the selection of drugs used for treatment, the route of drug administration, the combination therapy and the length of treatment (6).

Conclusion

In this study, we established that CRP, ESR and WBC were neither entirely sensitive nor specific for detecting UTIs or the localisation site of UTIs. The addition of other tests ensures the detection of UTIs and the localisation site of UTIs. A combination of laboratory tests (U/A, U/C, procalcitonin, urine migration inhibitory factor, urine interleukin-6, etc.) along with the history and exact clinical examination for the diagnosis of UTI as well as the localisation site are needed. In addition, the use of biomarkers may help to differentiate an upper UTI from a lower UTI and to avoid aggressive tests. Therefore, we suggest the use of more and newer supplemental tests alone or in combination for the final diagnosis of UTIs and for determining the localisation site of UTIs.

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Conflict of Interest

None.

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Authors' Contributions

Conception and design: PA, HJH
 Analysis and interpretation of the data: PA, AM, MMD
 Drafting of the article: PA
 Critical revision of the article for the important intellectual content: AM, NE
 Final approval of the article: HJH, MP
 Provision of study materials or patient: MMD
 Statistical expertise: HJH
 Administrative, technical or logistic support: NE
 Collection and assembly of data: NE, MP

Correspondence

Dr Parviz Ayazi
 MD (Qazvin University of Medical Sciences)
 Children Hospital Shahid beheshti Blvd
 Po Box 3415914595
 Qazvin, Iran
 Tel: +98-912-182 3797
 Fax: +98-281-334 4088
 E-mail: parviz_ayazi@yahoo.com

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