Predictive Accuracy of Urinary β2-Microglobulin for Kidney Injury in Children With Acute Pyelonephritis

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Introduction. Leukocyte count, erythrocyte sediment rate and C-reactive protein are available laboratory markers which may be helpful in prediction of technetium Tc 99m dimercaptosuccinic acid (DMSA) renal scintigraphy results. None of these, however, have enough accuracy for prediction of renal injury and scar. This study was aimed to evaluate the diagnostic accuracy of urinary β2-microglobulin in detection of renal injury in children with acute pyelonephritis.

Materials and Methods. Eighty-nine children between 2 months and 14 years old with the diagnosis of acute pyelonephritis that had no past history of infection in the urinary tract system were enrolled in the study. A standard urine sample according to patients' age was obtained for urine culture, urinalysis, and urinary β2-microglobulin tests. Blood sample was obtained for leukocyte count, creatinine, blood urea nitrogen, C-reactive protein, erythrocyte sediment rate, and electrolytes tests. All patients underwent DMSA scan.

Results. The cutoff point for urinary β2-microglubulin for prediction of positive DMSA scan was 0.8 mg with a sensitivity of 40.9% (95% CI, 26.3% to 56.8%) and a specificity of 84.1% (95% CI, 69.9% to 93.4%), a positive predictive value of 72.0% (95% CI, 50.6% to 87.9%) and an negative predictive value of 58.7% (95% CI, 45.6% to 71.0%).

Conclusions. Urinary β2-microglobulin is not enough sensitive and specific to be used as a diagnostic marker for prediction of renal injury. Other common markers such as erythrocyte sediment rate, leukocyte count, and C-reactive protein can be used in combination to predict kidney injury in children with acute pyelonephritis.

Original Paper

INTRODUCTION

Urinary Tract Infection (UTI) is one of the most common infections in childhood and infancy.[1] One of the most important complications of UTI is kidney injury, which results in hypertension, and end-stage renal disease in later decades of life.[2,3] Technetium Tc 99m dimercaptosuccinic acid (^{99m}Tc-DMSA) renal scintigraphy is widely used to determine the grade of scar and kidney injury in patients with acute pyelonephritis.[4] Some laboratory markers are also used for prediction of renal scar and kidney injury. Leukocyte count and erythrocyte sediment rate (ESR) are the available laboratory markers, which may be helpful in prediction of DMSA scan results.[5,6] Patients with higher ESR and leukocyte count are at a higher risk for kidney injury. Another marker which is usually used in qualitative measures is C-reactive

protein (CRP). Patients with positive CRP levels are at greater risk for development of renal scar.

None of the abovementioned markers have enough accuracy for prediction of renal injury. Therefore, researchers are trying new markers which may have better diagnostic accuracy for prediction of renal injury. Some researchers have reported the role of procalcitonin in the management of UTI and also in the prediction of renal scar.[7-9] β2-microglobulin is a low-molecular-weight protein which is freely filtered via glomerular membrane. β2-microglobulin is absorbed almost completely by the proximal tubules. Urinary β2-microglobulin level is an indicator of renal score. However, the sensitivity and specificity of it for detection of renal injury is not studied enough. In one study by Oh and colleagues,[10] the sensitivity and specificity for spot urinary β2-microglobulin were reported to be 78.7% and 90.1% for prediction of renal scar. Also for spot urinary β2-microglobulin-creatinine ratio, the sensitivity and specificity were 77.2% and 90.1%. Positive and negative predictive values were reported to be 72.7% and 90.1% for spot urinary β2-microglobulin and 73.9% and 91.6% for spot urinary β2-microglobulin-creatinine ratio, respectively. The authors concluded that spot urinary β2-microglobulin and spot urinary β2-microglobulin-creatinine ratio are more specific than leukocyte count, ESR, and CRP for prediction of renal scar.[10] Sharifian and colleagues concluded in their study that urinary β2-microglobulin is of prognostic value for renal scar in patients with pyelonephritis.[11] The aim of this study was to evaluate the diagnostic accuracy of urinary β2-microglobulin test in detection of renal injury in children with acute pyelonephritis.

MATERIALS AND METHODS

We carried out a descriptive cross-sectional study in 2012. The cohort included children between 2 months to 14 years old with a diagnosis of acute pyelonephritis who were referred as outpatient or for hospitalization to Koodakan Hospital, in Bandar Abbas, southern Iran, with no past history of infection in the urinary tract system. We selected 89 patients who had fever (38.5°C or higher) and positive urine culture (> 10^5 bacterial colony growth in 1 mL culture in midstream clean catheter and more than 10^3 colony count in sampling by catheter), but no urinary system anomalies, neurogenic bladder,

or history of surgery in the urinary tract system. A standard urine sample according to patients' age was obtained for urine culture, urinalysis, and urinary β2-microglobulin level tests. Also, a blood sample was obtained for complete blood count and measurement of creatinine, blood urea nitrogen, CRP, ESR, and electrolytes. All of the patients underwent DMSA renal scintigraphy in one center by a nuclear medicine specialist according to standard protocols. Patients were classified according to DMSA scan and urinary β2-microglobulin level was compared in each group.

Dimercaptosuccinic Acid Renal Scintigraphy

We performed DMSA scan using a Siemens E CAM 2009 device (Germany) in 1 step. Technetium was injected slowly intravenously in 4 to 5 minutes. All of the patients underwent imaging 3 hours after the injection of radio-drug. The patients were asked to use liquids and have urination during 3 hours expectation. Imaging was done in 4 aspects in about 5 minutes in the flat position. We asked the patients to be far from children and pregnant women for 24 hours. A modified grading system according to Itoh and colleagues[12] was used for DMSA scans: normal (grade 0), less than 2 renal contour defects (grade I), 2 renal contour defects but remnant areas of normal renal parenchyma (grade II), diffuse reduction in uptake throughout the whole kidney (grade III), shrunken kidney (grade IV), and indistinct margins of kidney (grade V).

Urinary β2-Microglobulin Measurement

A 15- to 20-mL urine sample was obtained from each patient for urinary β2-microglobulin measurement and was kept in 2°C to 8°C and was immediately transferred to laboratory. Urinary β2-microglobulin was measured using a Widas device (France) with automatic setting of alkaline pH 2 times for each sample. Unique laboratory kits were used for each sample.

Other Laboratory Tests

Complete blood count was done using a Sysmex KX-21N device (Japan), and ESR was measured using a Lendo device (Spain). Sodium and potassium levels were measured using an Eayslyte device (Norway), blood urea nitrogen and creatinine were measured using a Vital Lab Selectra, and CRP level was measured manually.

Statistical Analysis

Data were analyzed using the SPSS software (Statistical Package for the Social Sciences, version 20.0, SPSS Inc, Chicago, Ill, USA) and MedCalc software. Descriptive statistics including frequency, mean (95% confidence interval [CI]), and percentages were used for the report. The Kolmogorov-Smirnov test, Kruskal-Wallis test, Mann-Whitney test, and chi-square test were used, and the receiver operating characteristic (ROC) curve was used for estimation of specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV). *P* values less than .05 were assumed to be significant.

RESULTS

We studied 89 patients with acute pyelonephritis including 23 boys (25.8%) and 66 girls (74.2%). The mean age of the patients was 2.56 years (95% CI, 1.93 to 3.18 years). The mean hospitalization duration was calculated to be 4.09 days (95% CI, 3.32 to 4.86 days). Among the patients, 39 (43.8%) had active urinalysis. In 54 patients (60.7%), CRP was negative. Also, CRP was 1+, 2+, and 3+ in 2 (2.2%), 13 (14.6%), and 20 (22.5%), respectively. Urine culture results were not available for 2 patients (2.2%). Among the others, 41 (46.1%) had a positive culture and 46 (57.1%) had a negative culture result.

The mean urinary β2-microglobulin was 0.869 mg (95% CI, 0.60 mg to 1.13 mg). Urinary β2-microglobulin was not normally distributed in the study population. The median urinary β2-microglobulin level was significantly higher in the boys (1.62 mg/L; 95% CI, 0.32 mg/L to 2.59 mg/L) in comparison with the girls (0.19 mg/L; 95% CI, 0.13 mg/L to 0.29 mg/L; *P* < .001). Results of DMSA scan were unavailable for 1 patient (1.1%). Of the other patients, 44 (94.4%) had normal DMSA scan. Also, grade I, grade II, and grade III were reported in 15 (16.9%), 24 (27%), and 5 (5.6%) of

the patients, respectively. Table 1 summarizes the urinary β2-microglobulin level according to DMSA scan results in the patients studied. As shown in Figure 1, the differences in urinary β2-microglobulin levels were not significant between patients according to their DMSA scan (*P* = .27). No significant difference was found in β2-microglobulin level between the patients according to the CRP levels (*P* = .44; Table 2).

In patients with positive urine culture, the median urinary β2-microglobulin level was 0.20 mg/L (95% CI, 0.06 mg/L to 1.18 mg/L). Also in
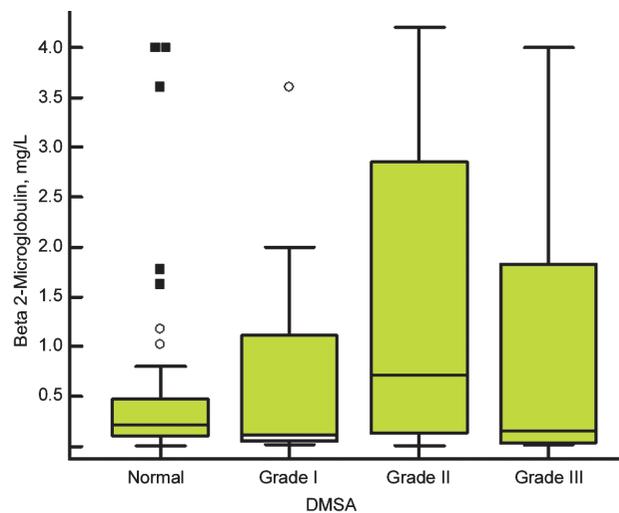
Table 1. Urinary β2-Microglobulin Level According to Dimercaptosuccinic Acid Scintigraphy

DMSA	Median	Mean	95% Confidence Interval	*P**
Normal	0.21 ± 0.98	0.58	0.28 to 0.8	< .001
Grade I	0.12 ± 1.01	0.65	0.09 to 1.21	.15
Grade II	0.71 ± 1.56	1.48	0.81 to 2.14	.08
Grade III	0.15 ± 1.70	1.06	-1.04 to 3.17	.65
All	0.23 ± 1.24	0.86	0.60 to 1.13	< .001

*Kolmogorov-Smirnov test for assessment of normality of the distribution of the data

Figure 1. Comparison of β2-microglobulin levels between Dimercaptosuccinic acid (DMSA) scintigraphy grades.

Table 2. Urinary β2-Microglobulin Level According to C-Reactive Protein Level

C-Reactive Protein	Median	Mean	95% Confidence Interval	*P**
Negative	0.22	0.77 ± 1.18	0.45 to 1.09	< .001
1+	0.30	0.30 ± 0.19	-1.41 to 2.02	> .99
2+	1.62	1.71 ± 1.67	0.7 to 2.73	.56
3+	0.19	0.63 ± 0.95	0.18 to 1.07	.10
All	0.23	0.86 ± 1.24	0.60 to 1.13	< .001

*Kolmogorov-Smirnov test for assessment of normality of the distribution of the data.

patients with negative culture, the median urinary β2-microglobulin level was 0.27 mg/L (95% CI, 0.17 mg/L to 0.44 mg/L). No significant difference was noted between the two groups (*P* = .36). No significant difference was seen in urinary β2-microglobulin levels between patients with active (0.18 mg/L; 95% CI 0.11 mg/L to 0.32 mg/L) and normal (0.36 mg/L; 95% CI, 0.20 mg/L to 0.56 mg/L) urinalysis (*P* = .28).

The ROC curve analysis was used in order to obtain a cutoff point for urinary β-2 microglobulin for prediction of DMSA scan results based on positive versus negative DMSA scan results. Figure 2 compares the ROC curve for urinary β2-microglobulin, leukocyte count, and ESR for prediction of DMSA scan results. The area under curve (AUC) was 0.556 (95% CI, 0.446 to 0.662; *P* = .38) for urinary β2-microglobulin. The cutoff point for urinary β2-microglobulin for prediction of positive DMSA scan was 0.8 mg/L with a sensitivity of 40.9% (95% CI, 26.3% to 56.8%) and a specificity of 84.1% (95% CI, 69.9% to 93.4%), a PPV of 72.0% (95% CI, 50.6% to 87.9%) and an NPV of 58.7% (95% CI, 45.6% to 71.0%). For leukocyte count, AUC was 0.599 (95% CI, 0.489 to 0.702; *P* = .11). The cutoff point for leukocyte count for prediction of DMSA scan was values greater than 12900×10^{12}/L with a sensitivity of 45.5% (95% CI, 30.4% to 61.2%) and a specificity of 84.1% (95% CI, 69.9% to 93.4%), a PPV of 74.1% (95% CI, 53.7% to 88.9%), and an NPV of 60.7% (95% CI, 47.3% to 72.9%). For ESR, the AUC was 0.629 (95% CI, 0.518 to 0.730; *P* = .03). The cutoff point for ESR for prediction of DMSA scan was values greater than 56 mm/h with a sensitivity of 31.8% (95% CI, 18.6% to 47.6%), a specificity of 97.6% (95% CI, 87.4% to 99.9%), a
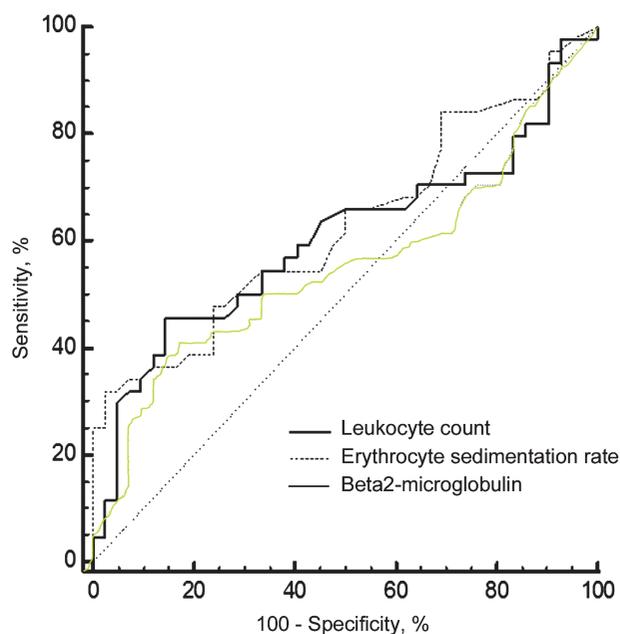

Figure 2. Receiver operating characteristic curves for β2-microglobulin, leukocyte count, and erythrocyte sedimentation rate for prediction of dimercaptosuccinic acid scintigraphy results.

PPV of 93.3% (95% CI, 68.1% to 99.8%), and an NPV of 57.7% (95% CI, 45.4% to 69.4%). Table 3 summarizes the sensitivity, specificity, PPV, and NPV of urinary β2-microglobulin, leukocyte, and ESR in prediction of DMSA scan results. Table 4 shows that in patients with acute pyelonephritis, higher CRP levels were associated with a higher risk of renal injury.

DISSCUSSION

Renal scar and injury is one of the most important complications of UTI. Its early diagnosis and treatment is very important. The DMSA scan is

Table 3. Diagnostic Accuracy of Urinary β2-Microglobulin, Leukocyte Count, and Erythrocyte Sedimentation Rate for Prediction of Dimercaptosuccinic Acid Scintigraphy Results

Diagnosis Test	Sensitivity	Specificity	Positive Predictive Value	Negative Predictive Value
Beta-2 microglobulin	40.91%	84.09%	72.0%	58.7%
Leukocyte count	45.45%	84.09%	74.1%	60.7%
Erythrocyte sedimentation rate	31.82%	97.62%	93.3%	57.7%

Table 4. Dimercaptosuccinic Acid Scintigraphy (DMSA) Results by C-Reactive Protein

| DMSA | C-Reactive Protein | | | | P | |
	Negative	1+	2+	3+	Trend	Correlation
Normal	33 (61.1)	2 (100)	4 (30.8)	5 (26.3)		
Abnormal	21 (38.9)	0	9 (69.2)	14 (73.7)		
Total	54 (100)	2 (100)	13 (100)	19 (100)	.003	.01

useful method for detection of renal scar and kidney injury.[13] However, this method is unavailable for all patients and should be requested according to indications. Some laboratory test helps us in order to detect high risk patients for kidney injury in order to request DMSA scan for them. Leukocyte count, ESR, and CRP are more common tests. However, new laboratory tests such as procalcitonin and urinary β2-microglobulin and also Doppler ultrasonography are shown to be able to predict DMSA scan results.[14]

Urinary β2-microglobulin excretion in urine is shown to be increased with the renal damage based on renal scan results and can be used for early diagnosis of acute pyelonephritis in children and is correlated with glomerular filtration rate.[15-19] It is also known as a noninvasive method for distinguishing upper and lower urinary tract infection.[20] Some studies have introduced urinary β2-microglobulin as the most reliable noninvasive method for detection of acute pyelonephritis.[21] This is due to the dysfunction of proximal tubule in upper urinary tract infections,[22] and can be used in early detection of kidney injury in patients with vesicourethral reflux.[23]

Sharifian and colleagues in a study in children with acute pyelonephritis have reported higher amounts of urinary β2-microglobulin-creatinine ratio in children with renal scar and poor outcome.[11] This study showed the predictive value of urinary β2-microglobulin for scar prediction in children with acute pyelonephritis. The authors in this study have not reported the specificity, sensitivity, NPV, and PPV of the markers in their study. Few studies have investigated the sensitivity, specificity, NPV, and PPV of urinary β2-microglobulin level in prediction of kidney injury in UTI children. In this study we have investigated the diagnostic accuracy of urinary β2-microglobulin in kidney injury. We also have compared the diagnostic accuracy of urinary β2-microglobulin with ESR and leukocyte count.

According to our results, leukocyte count is more sensitive and ESR is more specific in diagnosis of kidney injury. Also, the PPV is higher in both markers in comparison to urinary β2-microglobulin and also NPV is higher in leukocyte count in comparison to urinary β2-microglobulin.

One study by Oh and colleagues has reported higher specificity of urinary β2-microglobulin and macroglobulin-creatinine ratio in comparison to leukocyte count, ESR, and CRP in pediatric acute pyelonephritis. They reported the sensitivity, specificity, NPV, and PPV of 78.7%, 90.1%, 72.7%, and 90.1% for urinary β2-microglobulin. These amounts were 77.2%, 90.1%, 73.9%, and 91.6% for urinary β2-microglobulin-creatinine ratio. The sensitivity and specificity of ESR were 77.2% and 68.8%, respectively. The sensitivity, specificity, PPV, and NPV were 86.3%, 68.8%, 57.5% and 94%, respectively.[10]

Based on our results, it is not recommended to use urinary bet-2 microglobulin for prediction of renal scar because has more costs and is not available for all patients and all health centers. Also the prediction is more accurate using other simple tests such as ESR and leukocyte count. One possible explanation for our results is that excretion of urinary β2-microglobulin occurs in patients with renal scar when the glomerular filtration rate is severely decreased. In patients with earlier stages of renal injury or with mild renal injury the results of urinary β2-microglobulin test may be normal.[23] Also, we have used CRP in our study. In contrast with some studies which have used the quantitative measures of CRP, we have used the qualitative measures, because the routine method in our hospital is the qualitative method and is also available. We have shown that CRP level is associated with DMSA scan results and increase in CRP level is associated with higher risks of abnormal DMSA scan. Therefore, CRP can be used as another diagnostic marker for prediction of DMSA scan results.

CONCLUSIONS

Urinary β2-microglobulin is not enough sensitive and specific to be used as a diagnostic marker for prediction of renal injury. Other common markers such as ESR, leukocyte count, and CRP can be used in combination to predict kidney injury in children with UTI.

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CONFLICT OF INTEREST
None declared.

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