

Urinary Level of Interleukin-8 in Acute Pyelonephritis

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Abstract

Background and Aim: urinary tract infection is a prevalent disease in children. Determining the location of the bacterial invasion has a great impact on the treatment, follow-up, and complications. For this purpose, different laboratory and imaging methods are used, which are often invasive or unavailable. One of the non-invasive methods is to measure biomarkers such as interleukin-8 (IL-8) in the urine. The aim of this study was to evaluate the urinary level of interleukin-8 in acute pyelonephritis.

Methods: This cross-sectional study was carried out on 50 children aged 3-60 months. The children were divided into two groups. The first group included children with acute pyelonephritis and the second group included healthy children who were randomly selected as controls. Then, the urine levels of IL-8 and creatinine were measured.

Results: The mean age of the subjects in case and control groups was 17.5 ± 22 and 22.5 ± 18.2 months, respectively ($P = 0.92$).

The mean urinary ratio of IL-8/Cr in the patient and control groups was 161.7 ± 90.1 and 12.2 ± 19.6 Pgr/mgr respectively, indicating a significant difference ($P = 0.03$). The results showed that a urinary IL-8/Cr ratio of 32 pg/mg was diagnostic according to the Receiver Operating Curve (ROC).

Conclusion: Urinary IL-8/Cr ratio can be used for early diagnosis of acute pyelonephritis.

Keywords: Children; Diagnosis; Interleukin-8; Pyelonephritis.

Conflict of interest: The authors declare no conflict of interest.

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Introduction

Urinary tract infection (UTI) is a relatively common disease in infants and children. Its incidence is about 3-5% in girls and 1-2% in boys before puberty. Urinary tract infections are caused by various factors such as bacteria, viruses and fungi but they are often caused by bacteria, especially gram-negative bacteria like *E. coli*, in children without underlying diseases. The urinary tract consists of various parts, including the kidneys, ureters, bladder, and urethra. Therefore, it is important to determine the site and severity of bacterial invasion when diagnosing UTI (1-3).

The most important complication of a urinary tract infection is renal scarring, which is often caused by recurrent pyelonephritis. Renal scarring increases

the risk of late complications such as hypertension, chronic renal failure, and pregnancy complications in women. The distinction between pyelonephritis and cystitis is very important because the risk of developing renal scarring is high in pyelonephritis; as a result, work-up, type of treatment, duration of treatment, and follow-up are generally different in pyelonephritis and cystitis (2-4).

Determination of the site of infection and differentiating between acute pyelonephritis and cystitis are based on clinical signs, laboratory findings, and imaging. Many young children are unable to accurately express their symptoms. On the other hand, pyelonephritis often has no specific symptoms in infants such as fever without focus,

restlessness, anorexia, and gastroenteritis; therefore, it is difficult to diagnose acute pyelonephritis based on clinical symptoms in children. The use of laboratory findings such as CBC, ESR and CRP, although helpful, is not specific for urinary tract infections and the arbitrary use of antibiotics sometimes leads to false negative results in the urine culture. Imaging methods such as CT scan, DMSA, although accurate, are often unavailable, expensive, or invasive (3-6).

Therefore, the diagnosis of acute pyelonephritis in children is associated with certain problems that sometimes lead to lack of a diagnosis.

For this reason, researchers are always looking for newer and less invasive methods for diagnosing pyelonephritis, one of which is the use of biomarkers.

Several biomarkers such as NGAL, IL-6, IL-8, procalcitonin, and KIM-1 are used to diagnose UTI and monitor the progress of renal scarring (7-9).

Previous studies have focused more on the diagnostic value of IL-8 in urinary reflux or renal scars and less attention has been paid to its role in the diagnosis of pyelonephritis (10-12).

The aim of this study was to evaluate the urinary level of IL-8 as a non-invasive indicator in the diagnosis of pyelonephritis.

Methods

This cross-sectional-analytical study was adopted from a thesis of pediatrics nephrology subspecialty approved by Ethics Committee of Kermanshah University of Medical Sciences. Informed consent was obtained from the parents/legal guardians of all children.

The children were then divided into two groups. The first group included children with acute pyelonephritis and the second group included healthy children who were randomly selected as controls.

The patients were selected from outpatient clinics as well as patients admitted to the pediatric nephrology ward. Diagnosis of pyelonephritis was based on clinical signs (high fever, costovertebral angle pain, flank tenderness, nausea and vomiting, anorexia), urine analysis (pyuria, nitrite test, cast), positive urine culture, other laboratory findings [CBC (leukocytosis), positive CRP, high ESR] and sonography (to rule out other causes of fever and abdominal pain). In suspicious cases, a nuclear scan (DMSA scan) was used to confirm the diagnosis.

A combination of clinical and paraclinical findings was used to diagnose acute pyelonephritis and differentiate it from cystitis. In cases where a diagnosis of pyelonephritis was not confirmed despite the above measures, the patient was excluded from the study.

In order to reduce possible errors in the results, the patients with a history of underlying kidney diseases, urologic disorders, more than 3 days since the onset of clinical symptoms, and a history of antibiotic use in the last 7 days were excluded from the study.

A urine sample was taken measure IL-8 and creatinine levels before starting antibiotics. Urine samples were collected by urine bags in infants while clean-catch midstream urine samples were taken from older children.

The samples were stored at -20 C in a freezer until the sample size was complete. Then, they were thawed at room temperature to measure the creatinine and IL-8 levels using the Jaffe and ELISA (Sunquin kit) method, respectively. The ratio of IL-8 to creatinine was calculated to prevent the effect of urine concentration on the results.

The data were revised, coded and analyzed using SPSS software. Qualitative data are presented as frequency in table quantitative data are presented as mean $\pm$ SD. Chi-square was used to evaluate the correlation between qualitative variables, and independent sample t-test was applied to quantitative variables.

Results

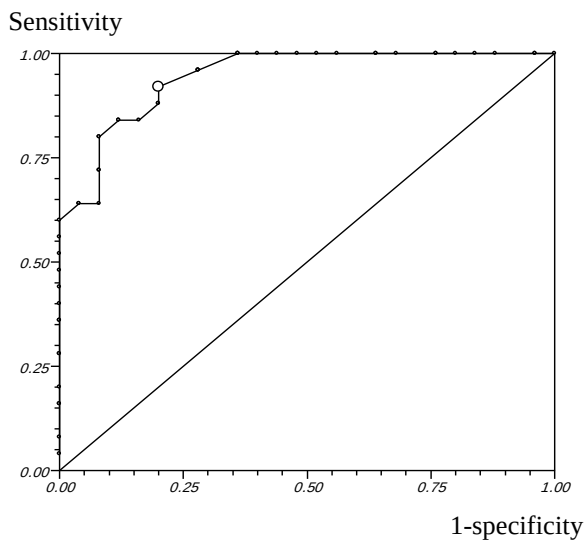
In this study, which was conducted over a period of one year, 50 children aged 3-60 months were investigated in two groups of patients and controls. In terms of sex distribution, 19 subjects were boys and 31 were girls (Table 1).

Chi-square did not show any significant difference in sex distribution between the two groups (P : 0.23). The min, max, and mean age of the subjects was 3, 54, and 22 ± 17.5 months in the patient group and 3, 60, months and 22.5 ± 18.2 months in the control group, respectively (P : 0.92).

The min, max, and mean IL-8/Cr ratio was 3.76, 291.6, and 161.7 ± 90.1 pgr/mgr in the patient group and 3.73, 58.5, and 19.6 ± 12.2 pgr/mgr in the control group respectively, indicating a significant difference between the two groups (P : 0.03). According to the Receiver Operating Curve (ROC) analysis, a urinary IL-8/Cr level of 32 pg/mg was diagnostic (Figure 1).

Table-1. Sex distribution of study groups

Ggender	Group1	Group2	total
Male	7(28%)	12(48%)	19(38%)
Female	18(72%)	13(52%)	31(62%)
total	25	25	50(100%)

**Figure 1.** ROC curve of UIL-8/Cr level

Discussion

Pyelonephritis is a common childhood infections and one of the major causes of fever without focus in infants, which can damage the renal parenchyma and cause scar formation if not diagnosed and treated properly. Because of difficulty in proper and prompt diagnosis of pyelonephritis in children, it sometimes causes a diagnostic challenge (4-9).

In the present study, the urinary level of IL-8 was measured in 50 children aged 3-60 months. The IL-8/Cr ratio was significantly higher in the patient group compared to the control group ($P = 0.03$) and a urinary IL-8/Cr ratio of 32 pg/mg was found to be diagnostic.

It is necessary to use newer methods for diagnosis of pyelonephritis. One of these methods is measurement of biomarkers such as interleukin 8 in the urine. Interleukin 8 (IL-8) is a cytokine with a protein structure that is secreted into the urine by the

epithelial cells of the urinary tract in response to infection and various inflammatory stimuli. It has chemotactic effects and causes the accumulation of inflammatory cells in the urine and pyuria (10-15). A similar study by Benson et al. on IL-6 and IL-8 in Sweden showed that the urinary levels of these biomarkers increased in urinary tract infections. Importantly, the increase in IL-8 was not affected by age (16).

In another study conducted by Taninmis et al. in Turkey in 2016, measurement of urine IL-8 was found to be useful for early detection of pyelonephritis (17). In 2016, Krzemien et al. found that the IL-8 urinary level was significantly higher in urinary tract infection (18).

Valdimarsson et al. examined eight different biomarkers in the urine in Sweden in 2017 and found that among various biomarkers, NGAL and IL-8 were the best biomarkers for diagnosis of febrile urinary tract infections (7).

The findings of these studies are all consistent with the results of the present study.

Because a DMSA scan was not performed for follow up of the patients in the present study, it is impossible to draw a conclusion on the relationship between kidney damage and the risk of developing renal scarring in the future using the IL-8 urinary level.

The most important limitations of this study were its small sample size and the impossibility of performing DMSA scans for all patients. Studies with larger sample sizes and patient selection based on nuclear scan can provide more reliable results.

Conclusion

The IL-8/Cr ratio in the urine can help to diagnose pyelonephritis more accurately in patients suspected of urinary tract infection with nonspecific clinical symptoms or a false negative urine culture.

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Conflict of Interest

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