Demographic, clinical, and laboratory factors associated with renal parenchymal injury in Iranian children with acute pyelonephritis

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Abstract

Background: The association between renal parenchyma changes on dimercaptosuccinic acid (DMSA) scans and demographic, clinical, and laboratory markers was assessed in pediatric patients with acute pyelonephritis.

Methods: A retrospective study of 67 Iranian babies and children aged 1-month to 12-year with APN was conducted between 2012 and 2018. The presence of renal parenchymal involvement (RPI) during APN was determined using technetium-99m DMSA during the first 2 weeks of hospitalization. The association of DMSA results with demographic data, clinical features (hospitalization stay, fever temperature and duration), and laboratory parameters such as pathogen type, and hematological factors (ESR, CRP, BUN, Cr, Hb, and WBC) was evaluated.

Results: 92.5% of children with an average age of 43.76 ± 5.2 months were girls. Twenty-four children (35.8%) did not have renal parenchymal injury (RPI), while 26 (38.8%) and 17 (25.4%) patients showed RPI in one and both kidneys, respectively. There was no significant association between RPI and mean ESR, CRP, BUN, and WBC. However, there were significant associations between RPI and higher mean levels of Cr, Hb, and BMI.

Conclusions: Low BMI and Hb levels and increased Cr levels might be indicative of the presence of RPI in children with APN.

Keywords: Acute pyelonephritis, Children, Renal scan, Tc-99m DMSA, Laboratory markers

Background

Urinary tract infection (UTI) is one of the most common childhood bacterial diseases worldwide [1–3]. It is more prevalent in girls than boys [4]. Upper UTI could cause renal parenchymal injury (RPI) and subsequent progression to formation of renal parenchymal scars. Moreover, UTI increases the level of stress and anxiety among children and their parents [1, 5, 6]. UTI can involve the upper tract especially kidneys (acute pyelonephritis (APN)) and/or the lower urinary tract including urethra (urethritis) or the bladder (cystitis) [2–4]. However, it is difficult to discriminate them from each other in babies and young children based on clinical symptoms and laboratory results [7]. Finding the proper methodologies for timely diagnosis and treatment is essential because any delay significantly increases the risk of complications such as hypertension, preeclampsia, growth retardation, and progressive kidney scarring and failure later in life [8–10].

Researchers have been looking for affordable and accessible markers with maximum sensitivity and specificity and the least invasive to predict UTI with RPI. The differentiation between upper and lower UTIs, the tracing...
of abnormalities, and the implementation of appropriate follow-up measures among pediatric patients have been made possible recently [11–13]. Technetium-99m dimer-captosuccinic acid (Tc-99m DMSA) is a standard imaging technique to diagnose RPI [14, 15]. The technique contributes to the definitive assessment of separate kidney function and total radionuclide uptake. A reduction in the radionuclide uptake can be observed in the damaged locations of kidneys. However, if a DMSA scan is normal during a febrile UTI, no scarring will result from that infection [16]. It could also be used to identify the extent of the RPI in the acute phase and on subsequent follow-up [17].

Factors associated with the risk of RPI in children with APN include gender, age, urinary abnormalities (especially vesicoureteral reflux (VUR)), bacterial virulence, recurrence of infection, and bladder dysfunction [18]. Renal parenchymal damage is significantly associated with an increase in levels of laboratory markers of inflammation such as white blood cells (WBCs), erythrocyte sedimentation rate (ESR), and C-reactive protein (CRP) [15, 19]. Accordingly, it seems that the comparison of demographic and laboratory markers with Tc-99m DMSA scans can contribute to an understanding of the risk factors that are predictive of the presence of RPI in children with APN and could therefore serve as early prognostic parameters. Therefore, this 10-year retrospective study aimed to explore the relationships between demographic, clinical, and laboratory indicators and renal DMSA scans of Iranian babies and children with febrile UTI.

**Methods**

**Study design and subjects**

This study was retrospectively conducted based on the data census of all pediatric patients with APN. All the patients were admitted to Bahrami Hospital (Tehran, Iran), affiliated with Tehran University of Medical Sciences (TUMS), between March 2012 and March 2018. A total of 67 children with APN were evaluated. Verbal and written informed consent was obtained from their parents using phone contact and face-to-face interview methods. Each child had a single code number to maintain the confidentiality of participants’ data. The research procedure was entirely consistent with the Human Ethics Committee of the TUMS.

**Inclusion and exclusion criteria**

All 1-month to 12-year-old patients with APN admitted to Bahrami Hospital were included in the study. The criteria for diagnosis of pyelonephritis included axillary temperatures of over 38.5 °C, poor general condition as indicated by presence of abdominal and flank pains, vomiting, and agitation [20], and positive urine culture (PUC). A PUC was defined as presence of colony count in midstream urine sample more than or equal to 10^{5} CFU/mL of a single pathogen, or ≥ 10^{3} CFU/mL in urine sample obtained by catheter method, or ≥ 10^{8} Gram-positive bacteria or any number of gram-negative bacteria in urine obtained by suprapubic aspiration (SPA) [21]. Suprapubic aspiration was carried out in babies and children aged 1 month–1.5 years of age, catheterization in 1.5–4 years of age, and clean catch urine collection (Quick-Wee) in 4.5–12 years old [22]. Children with all three criteria were included in the study, while patients with a history of urinary reflux, VUR, urinary tract surgery, urinary tract abnormality, or previous renal scar (presence of photopenic areas with shrinkage and thinning of the renal cortex on DMSA scan), and any pre-existing malformations were excluded.

**Data collection**

The medical information of the patients was collected from archived electronic files available from March 2012 to March 2018. The keyword “pyelonephritis” was first searched to prepare a list of patients. After ensuring the accuracy of pyelonephritis diagnosis, the necessary information was extracted by referring to the history, disease course, and summary of patients’ files. The RPI severity during acute febrile UTI using the Tc-99m DMSA was that determined at the first 2 weeks of hospitalization. If the hospital records contained the necessary information, the patients’ clinic records were studied to extract their DMSA scan related-information. If the DMSA scan data was ambiguous or insufficient, the patient’s parents and specialists were contacted. This DMSA scan information was divided into three groups: (I) patients with normal kidney scans or without RPI (n = 24), (II) patients with RPI in one kidney (n = 26), and (III) patients with abnormal scans in both kidneys (n = 17). In this study, the association of severity of involvement of each of the left and right kidneys in groups II and III with body mass index (BMI), glomerular filtration rate (GFR), and other laboratory factors (ESR > 20 mm/h, CRP > 10 mg/L, leukocytosis (WBCs > 11 × 10^{9}/L), and anemia [hemoglobin (Hb) < 10.5 g/dL]) was separately determined [19, 22, 23]. The Kirby–Bauer disk diffusion method was used to assess the antibiotic susceptibility of the bacterial isolates [24].

All the information on eligible patients was imported to pre-prepared questionnaires. The data collected included age, gender, height, weight, BMI, fever degree, duration of fever before and after treatment, duration of hospital stay (HS), and results of urine culture, blood urea nitrogen (BUN), serum creatinine (SCr), Hb, WBCs, CRP, ESR, and estimated GFR (eGFR). The kidney
function level at the time of admission was assessed by
determination of the eGFR (mL/min/1.73 m²) using the
following equation [25]:
\[ eGFR = \frac{141 \times \text{Height(cm)}}{0.413 \times \text{SCr(mg/dL)}} \]

As the level of SCr in children is dependent on their
age and gender, this biochemical marker was normalized
with the median SCr value at the corresponding age and
gender. The body height of children was measured using
a stadiometer with an accuracy of 0.1 cm. An infantom-
eter was used to measure the recumbent length of young
children (<24 months old). The body weight was meas-
ured by wearing light clothes and no shoes or socks using
a standard electronic balance with an accuracy of 0.01 g.
The BMI was determined by dividing the weight (in Kg)
divided by the square of height (in m).

Data analysis
The data at a significant level of p < 0.05 were analyzed
using the SPSS software package version 21.0 (SPSS Inc.,
Chicago, IL, USA). The descriptive data are represented
as frequencies, percentages, and means ± standard devia-
tions. The significance of differences between means and
frequencies was assessed using independent t-test (con-
tinuous variables) and Chi-square (\(\chi^2\), categorical vari-
bles). Multiple means were compared using analysis of
variance (ANOVA). A multiple logistic regression analy-
thesis was carried out to assess the independence of
parameters revealed that the strongest association was
with BMI and SCr levels (p < 0.05; \(r = 0.894\)).

The patients had a PUC with six pathogen types. As
expected, *Escherichia coli* was the most frequent patho-
gen and was isolated in 89.4% urine samples. The other
bacterial species were Gram-negative bacilli (n = 2;
3.03%), *Klebsiella pneumoniae* (n = 2; 3.03%), *Acinetobacter*
(n = 1; 1.51%), *Enterococcus* (n = 1; 1.51%), and
Group B *Streptococcus* (n = 1; 1.51%). There was no sig-
nificant association between LKCs and bacterial species.
There were three girls with recurrent UTI (4.5%), and *E.
coli* was the isolate from these children. The antibiotic
susceptibility of the *E. coli* isolates showed the highest
prevalence of resistance to ampicillin (87.2%) and cotri-
moxazole (83.2%), while the highest prevalence of sensi-
tivity was to gentamicin (75.1%) and imipenem (72.9%).

Results
Sixty-seven infants and children, 5 boys (7.5%) and 62
girls (92.5%) were included in the study. Overall, 43
(64.2%) had renal parenchymal involvement, RPI, on
DMSA scan while 24 (35.8%) did not. Among those with
RPI (n = 43), it was unilateral in 26 children (60.5%) and
bilateral in 17 (39.5). Among those with unilateral RPI
(n = 26), the left kidney was involved in in all 5 boys, and
in only 28 (45.2%) of the 62 girls (p = 0.049), while right
kidney involvement was present in 1/5 (20.0%) versus
26/62 (41.9%; p = 0.647).

The differences in demographic, clinical and labora-
tory indices between children with versus without RPI,
children with involvement of left versus right versus
both kidneys, and those with unilateral versus bilateral
involvement are set out in Tables 1 and 2. Table 1 features
the differences in means plus/minus standard deviations
and Table 2 the differences in frequencies and propor-
tions. The only significant differences were in BMI, and
serum creatinine and hemoglobin levels (Tables 1 and
2). Children with RPI had a significantly lower mean
BMI (p = 0.045) and higher number with abnormal
BNI (p = 0.038), a higher mean serum creatinine level
(p = 0.034) and higher number with abnormal levels
(p = 0.042), and lower hemoglobin level (p = 0.048) and
higher number with anemia (hemoglobin level < 10.5 g/
dL [22, 23]; p = 0.035). Those with bilateral RPI simi-
larly had a significantly lower mean BMI (p = 0.039) and
higher number with abnormal BNI (p = 0.029), a higher
mean serum creatinine level (p = 0.044) and higher num-
ber with abnormal levels (p = 0.045), and lower hemo-
globin level (p = 0.045) and higher number with anemia
(hemoglobin level < 10.5 g/dL [22, 23]; p = 0.040).

Table 3 shows that the order of effectiveness of predic-
tors associated with the presence of abnormalities on
renal scan changes among the children with APN was
Hb (anemia) > SCr > BMI. The correlation results of these
parameters revealed that the strongest association was
with BMI and SCr levels (p < 0.05; \(r = 0.894\)).

Discussion
Our findings showed that both the presence (RPI present
versus absent) and pattern (unilateral versus bilateral RPI,
and RPI in left versus right kidney) of RPI as diagnosed
using DMSA scans had significant associations with only
three factors including BMI, SCr, and hemoglobin level.

Obesity is associated with an increased risk of febrile
UTI and APN [26–29]. The high BMI in obese chil-
dren can negatively affect the function of immune cells
through the generation of chronic low-grade systemic
inflammation, changes in the complex interactions of
adipokines, immune cells, and cellular metabolism, as
well as epigenetic changes. The dysregulation of immune
responses disturbs the normal balance of sympathetic
and parasympathetic activity to control voiding and urine
storage and leads to UTI or APN [26]. 60–65% of patients
with febrile UTIs may have APN [30]. We however found
that children with LKCs and bilateral RPI have lower
BMI values than those with normal DMSA scans. Thus,
low BMI could be also a significant risk factor for UTI
and development of severe infection with RPI in children.
Table 1  Mean of demographic, clinical, and laboratory indices in relation to presence and pattern of abnormalities on DMSA scan

| Demographic/Clinical factora | DMSA scansb | p-value | DMSA scansb | p-value | DMSA scansb | p-value |
|-----------------------------|-------------|---------|-------------|---------|-------------|---------|
|                             | RPI (Abnormal, n = 43) | No RPI (Normal, n = 24) | RPI in LKCs (n = 14) | RPI in RKCs (n = 12) | RPI in both (n = 17) | Unilateral (n = 26) RPI | Bilateral (n = 17) RPI |
| Age (month)                 | 46.56 ± 42.58  | 38.75 ± 33.61  | 0.477 | 46.10 ± 32.31  | 45.97 ± 25.69  | 47.52 ± 18.51  | 0.821 | 46.04 ± 29.52  | 47.52 ± 18.51  | 0.852 |
| BMI (kg/m²)                 | 16.06 ± 1.99b | 17.37 ± 3.24a | 0.045* | 15.90 ± 2.74a | 16.47 ± 1.61a  | 14.08 ± 1.74b | 0.041* | 16.17 ± 1.70a | 14.08 ± 1.74b | 0.039* |
| Fever (°C)                  | 38.85 ± 0.51  | 38.86 ± 0.43  | 0.972 | 38.93 ± 0.61  | 38.86 ± 0.49  | 38.91 ± 0.42  | 0.905 | 38.89 ± 0.43  | 38.91 ± 0.42  | 0.916 |
| HS (day)                    | 4.95 ± 2.80   | 4.50 ± 2.43   | 0.509 | 5.12 ± 1.78   | 4.81 ± 2.09   | 5.05 ± 3.20   | 0.532 | 5.52 ± 2.42   | 5.05 ± 3.20   | 0.608 |
| ESR (mm/h)                  | 49.55 ± 29.54 | 47.84 ± 24.11 | 0.728 | 41.65 ± 16.58 | 44.09 ± 21.36 | 38.95 ± 24.60 | 0.053 | 42.77 ± 18.53 | 38.95 ± 24.61 | 0.0062 |
| CRP (mg/L)                  | 56.90 ± 37.59 | 59.45 ± 33.28 | 0.784 | 58.54 ± 32.14 | 56.36 ± 34.21 | 59.40 ± 41.70 | 0.755 | 57.53 ± 35.79 | 59.40 ± 41.73 | 0.0689 |
| WBC (× 10⁹/L)               | 14.21 ± 5.40  | 13.35 ± 5.18  | 0.528 | 13.51 ± 4.92  | 13.29 ± 5.23  | 14.75 ± 4.50  | 0.092 | 13.40 ± 5.92  | 14.75 ± 4.50  | 0.796 |
| Hb (g/dL)                   | 10.77 ± 1.26  | 11.21 ± 1.08  | 0.161 | 10.72 ± 1.05  | 10.81 ± 1.07  | 10.83 ± 1.50  | 0.212 | 10.76 ± 1.35  | 10.83 ± 1.50  | 0.405 |
| BUN (mg/dL)                 | 12.20 ± 5.21  | 11.37 ± 3.97  | 0.465 | 12.86 ± 5.84  | 11.77 ± 6.02  | 12.79 ± 5.35  | 0.422 | 12.35 ± 5.32  | 12.79 ± 5.35  | 0.523 |
| Scr (mg/dL)                 | 0.60 ± 0.16a  | 0.54 ± 0.09b  | 0.034* | 0.63 ± 0.03a  | 0.58 ± 0.02b  | 0.55 ± 0.15b  | 0.047* | 0.61 ± 0.09a  | 0.55 ± 0.15  | 0.044* |
| eGFR (ml/min/1.73 m²)       | 65.87 ± 16.25 | 66.72 ± 14.76 | 0.829 | 66.67 ± 9.75  | 64.40 ± 11.01 | 63.38 ± 14.74 | 0.836 | 65.60 ± 15.33 | 63.38 ± 14.74 | 0.0687 |
| Hb (g/dL)                   | 11.1 ± 0.9a   | 11.8 ± 1.2b   | 0.048* | 10.4 ± 0.6a   | 10.9 ± 0.8b   | 11.2 ± 0.8b   | 0.049* | 10.6 ± 0.7a   | 11.2 ± 0.8b   | 0.045* |

*p-values less than 0.05 are statistically significant

BMI: body mass index, HS: hospitalization stay, ESR: erythrocyte sedimentation rate, CRP: C-reactive protein, WBC: white blood cell, Hb: hemoglobin, BUN: blood urea nitrogen, Scr: serum creatinine, eGFR: estimated glomerular filtration rate

RPI: renal parenchymal injury, LKCs: left kidney changes, RKCs: right kidney changes
Table 2  Relationship between the frequency of abnormal clinical/laboratory indices and presence versus absence of RPI, and pattern of RPI (left versus right versus both kidneys, and unilateral versus bilateral)

| Demographic/clinical factor | DMSA scansb | p-value | DMSA scansb | p-value | DMSA scansb | p-value |
|----------------------------|-------------|---------|-------------|---------|-------------|---------|
|                            | RPI (Abnormal, n = 43) | No RPI (Normal, n = 24) | RPI in LKCs (n = 14) | RPI in RKCs (n = 12) | RPI in both (n = 17) | RPI in both (n = 17) |
| BMI (kg/m²)                | 24 (55.8)   | 7 (29.2) | 0.038*      | 6 (42.8)   | 6 (50)   | 12 (70.6) | 0.033*   |
| Fever duration (BT)        | 12 (27.9)   | 5 (25)  | 0.051       | 4 (28.6)   | 3 (25)   | 5 (29.4) | 0.662    |
| Fever duration (AT)        | 3 (7)       | 1 (4.1) | 0.754       | 1 (7.1)    | 1 (8.3)  | 1 (5.9)  | 0.546    |
| ESR (mm/h)                 | 7 (16.3)    | 3 (12.5) | 0.125      | 2 (14.3)   | 2 (16.7) | 3 (17.6) | 0.607    |
| CRP (mg/L)                 | 2 (4.7)     | 1 (4.2) | 0.711       | 1 (7.1)    | 0 (0)    | 1 (5.9)  | 0.094    |
| WBC (*10⁹/L)               | 7 (16.3)    | 4 (16.7) | 0.803      | 2 (14.3)   | 2 (16.7) | 3 (17.6) | 0.607    |
| Hb (g/dL)                  | 3 (7)       | 2 (8.3) | 0.072       | 1 (7.1)    | 1 (8.3)  | 1 (5.9)  | 0.546    |
| BUN (mg/dL)                | 6 (14)      | 4 (16.7) | 0.314      | 2 (14.3)   | 2 (16.7) | 3 (11.8) | 0.056    |
| SCr (mg/dL)                | 10 (23.3)   | 3 (12.5) | 0.042*     | 2 (14.3)   | 4 (33.3) | 4 (23.5) | 0.039*   |
| eGFR (mL/min/1.73 m²)      | 4 (9.3)     | 2 (8.3) | 0.772       | 1 (7.1)    | 1 (8.3)  | 1 (5.9)  | 0.546    |
| Anemia (Hb < 10.5 g/dL %)  | 11 (25.6)   | 3 (12)  | 0.035*      | 6 (42.8)   | 2 (16.6) | 3 (17.6) | 0.036*   |

Frequencies are expressed as number (percentage)

* p-values less than 0.05 are statistically significant

BMI body mass index, BT/AT before/after treatment, ESR erythrocyte sedimentation rate, CRP C-reactive protein, WBC white blood cell, Hb hemoglobin, BUN blood urea nitrogen, SCr serum creatinine, eGFR estimated glomerular filtration rate

Bilateral renal parenchymal injury, LKCs left kidney changes, RKCs right kidney changes
in developing countries (such as Iran), probably reflecting malnutrition and poor hygiene standards. The weak immunity among undernourished persons has been attributed to the depleted leucocyte, lymphocyte, and T-cell counts, increased CD4/CD8 ratios, and decreased CD2/CD19 ratios [31, 32]. However, optimal antimicrobial therapy may improve the BMI effect on the gut microbiota [27, 33], and the linkage between changed gut microbiota and human metabolism [34], as well as bone growth and development [35].

There was a significant association between the presence of renal parenchyma changes and increased SCr. Similarly, Ataei et al. [36] reported a significant correlation between renal parenchyma changes and increased SCr, but Amaral et al. [37] did not report any. This discrepancy may be due to the unbalanced alterations in muscle mass and tubular secretion and their effects on the SCr levels [38]. Breinbjerg et al. [39] also found that even non- 

| Variables | Beta     | Odds ratio | 95% CI          | p-value |
|-----------|----------|------------|-----------------|---------|
| BMI       | 0.314    | 1.368      | 0.932–1.614     | 0.0411  |
| Hb        | −0.693   | 0.500      | 0.276–0.805     | 0.0193  |
| SCr       | 3.689    | 40.004     | 0.598–2579.1    | 0.0367  |

Dependent variable: DMSA renal scan changes (positive: 1, negative: 0)

Conclusions

We conclude that a lower BMI, higher SCr, and anemia are significantly associated with the presence of RPI in children with febrile UTI. Evaluating these demographic and laboratory features might be helpful to identify pediatric patients with APN who require a close follow-up of renal function.

Abbreviations

APN: Acute pyelonephritis; BMI: Body mass index; BUN: Blood urea nitrogen; CRP: C-reactive protein; ESR: Erythrocyte sedimentation rate; eGFR: Estimated glomerular filtration rate; Hb: Hemoglobin; HS: Hospitalization stay; (R) PI: (Renal) parenchymal involvement; RKCs: Right kidney changes; SCr: Serum creatinine; Tc-99m DMSA: Technetium-99m dimercaptosuccinic acid; UTI: Urinary tract infection; VUR: Vesicoureteral reflux; WBCs: White blood cells.

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Authors’ contributions

ZB and OF performed research and analyzed data, SYM, AA, and MJ designed research, interpreted the data, and critically reviewed the manuscript; LX, EHB, MK, and AI drafted the work and substantively contributed to scientific editions and discussions. All authors read and approved the final manuscript.

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Availability of data and materials

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

Ethics approval and consent to participate
The study’s protocol with an ethical code of IR.TUMS.MEDICINE.REC.1397.759 was approved by the Ethics Committee of Tehran University of Medical Sciences (Tehran, Iran), and all methods were performed following the relevant guidelines and regulations. The verbal and written informed consent was obtained from all the children and their parents or legal guardian before implementing this study.

Consent for publication
Not applicable.

Competing interests
The authors declare that they have no conflict of interests.

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