

## Research Article

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# Screening for Vesico-ureteral Reflux and Renal Scar in Patients With Urinary Tract Infection

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**Introduction:** The aim of this study was to assess different grades of VUR and renal scar in children presented with single or recurrent episodes of UTI.

**Material and Methods:** Thirty-six children aged one month to 16 years with single or recurrent episodes of UTI were enrolled in this prospective descriptive study performed from July 2012 to June 2013. Grading of vesico-ureteric reflux, renal cortical scar and their co-relation in children presented with UTI were the outcome variables.

**Results:** Of 36 patients, 33 (91.6%) were male and 3 (8.4%) female. Patients were divided into three groups based on their age (<12 months, 12-60 months and older than 60 months). VUR was detected in 37 (51.39%) renal units among all the group of patients evaluated for UTI. Mild reflux (grades I and II) was found in 2 (2.78%), moderate in 9 (12.5%) and severe in 26 (36.11%) patients. Of 72 kidney units, 37 kidney units had different grades of cortical scar. Grades I & II renal scar found in 12 (33.33%) patients in the right kidney and 14 (38.88%) in the left kidney. Higher grades of scar (grades III & IV) were found in the right kidney and the left kidney in 5 (13.88%) and 6 (16.66%) patients, respectively. A positive co-relation was observed between grades of reflux and grades of renal scars (for the right kidney  $r = +0.670$ ,  $p < 0.01$ ; the left kidney  $r = +0.700$ ,  $p < 0.01$ ).

**Conclusions:** Higher grades of renal scar were directly related in children with male sex, younger age and having higher grades of VUR.

**Keywords:** Renal Scar; Urinary tract infection; Vesico-Ureteral reflux.

**Running Title:** Screening for Vesico-ureteral Reflux and Renal Scar in UTI

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## Introduction

Urinary tract infection (UTI) is a leading cause of childhood morbidity and is one of the commonest renal diseases in childhood [1-3]. In children, UTI may serve as an important marker of structural or functional urinary tract abnormalities.

Though, UTI may be the first symptom of obstructive uropathy or bladder dysfunction, the

most common abnormality heralded by UTI is vesico-ureteral reflux [4]. Vesico ureteral reflux (VUR) is an abnormal condition of the urinary system in which urine flows in the reverse direction, from the bladder to the kidney, through the ureter. It can affect either one or both ureters. It is one of the commonest urological anomalies in children [5]. The exact incidence of VUR is not

known, because it is not feasible to do voiding cystourethrogram (VCUG) in a large cohort of healthy children. Its prevalence varies from 1.3% of healthy children [6] to 8-50% of children evaluated after UTI [7]. In newborn and infants, the incidence of VUR after diagnosis of UTI is 36-49% [8]. VUR can vary in severity and is classified from grade I, as mild, to grade V, as severe (Figure 1). On the other hand, renal cortical scar may occur by either recurrent UTI with VUR or VUR without UTI, irrespective of their grading.

Renal scarring is associated with its fatal consequence like chronic kidney disease (CKD) in children. Children with higher grade of VUR have an increased likelihood of developing renal scarring [9]. The International reflux study reported that renal injury is more frequent in children less than two years with high grade VUR [10]. Therefore, evaluation of reflux and associated scarring is of paramount importance, particularly in younger age, who are more prone to develop such fatal consequences.

Ultrasonography (USG) is the initial modality for the evaluation of post-natal hydronephrosis and UTI in children [4]. USG has been used to detect VUR successfully in high grades of VUR in several studies, but it failed to detect lower grades in many studies [11]. That is why VCUG is the primary diagnostic modality for identifying VUR. For diagnosing renal scar, dimercaptosuccinic acid renal scan (DMSA Renal Scan) is currently the accepted gold standard [12].

Though, this is an important issue, there are a few studies about VUR and renal scarring in our country. Therefore, this study was designed to assess different grades of VUR and renal scarring in children admitted with single or recurrent episodes of UTI.

## Materials and Methods

This prospective descriptive study was performed in the Department of Pediatric Nephrology, Bangabandhu Sheikh Mujib Medical University (BSMMU), Dhaka, Bangladesh over a period of one year from July 2012 to June 2013. Prior to the study, approval of the ethical review board of BSMMU was taken. Thirty-six children from one month to 16 years with single or recurrent episodes of UTI admitted in the Pediatric Nephrology department were enrolled in this study. UTI was considered when children presented with fever, abdominal pain, vomiting, frequency and urgency of micturition with either suprapubic or renal angle tenderness for the first

time or recurrent episodes along with Urine pus cell >5/HPF in urine analysis. Recurrent UTI was defined as culture positive UTI at least two episodes within six months or three episodes in one year period. UTI was confirmed when a single pathogenic organism was detected by urine culture at a concentration of  $1 \times 10^5$ /mL or more in a clean catch mid-stream urine sample or by urobag collection and any single pathogen in suprapubic puncture. Five milliliters (5mL) of the sample inoculated on a blood agar and Cysteine lysine electrolyte deficient (CLED) agar plates. The blood agar plate was incubated aerobically for 18-24 hours at 37°C. Identification of the organisms was performed by standard biochemical methods. Ultrasonography (USG) of Kidney Ureter and Bladder (KUB) with post-voided residue (PVR) was performed for all enrolled patients. USG was performed by 2D machine with curvilinear probe (resolution 3.5MHz). All children with proved UTI underwent micturiting cystourethrogram (MCUG) at the end of antimicrobial therapy for 10-14 days or after urine became sterile by urinalysis or proven by culture. The procedure was performed by installation of Lopamiro through catheter into the bladder; anterior, full bladder and micturiting snaps were taken. Vesico-ureteral reflux was determined by MCUG and graded according to the international society of VUR.

Dimercaptosuccinic acid (DMSA) renal scan was performed for each patient within two weeks after confirmation of diagnosis. The scan was performed by injection of technetium99 dimercaptosuccinic acid and six (anterior, posterior, right anterior oblique, left anterior oblique, left anterior oblique and left posterior oblique) views were taken by low energy high resolution gamma camera, keeping the patient in prone position. Renal scar was defined by focal or diffuse areas of diminished uptake of isotopes. Renal scar was reviewed and graded by a nuclear radiologist of the Institute of Nuclear Medicine (INM).

Children with recurrent UTI were evaluated by lumbosacral spine X-ray to exclude spina-bifida or spinal dysraphism. Other relevant assessments like CBC, ESR, C-reactive protein and renal function test were performed for each patient.

Collected data was analyzed by Chi-square test and Pearson's co-relation co-efficient test using SPSS software version 16 to measure the level of statistical significance. P-value less than 0.05 was considered as the level of significance.

**Results**

Among 36 patients recruited, 33 (91.6%) were male and 3 (8.4%) female. Their mean age at presentation was 49.50 ± 48.2 months (ranged 2 to 168 months). Patients were divided into three groups based on their age (<12 months, 12-60 months and >60 months). Among them, 7 (19.4%) were in < 12 month group, 19 (52.8%) in 12-60 month group and 10 (27.8%) in >60 month group (Table 1).

**Table 1.** Age and sex distribution of the study population (n=36)

Age (month)	Children no. (%)	Age (month) Mean ± SD	Range
<12	7 (19.4)	6.71±3.82	2-11
12-60	19 (52.8)	27.53±14.18	12-57
>60	10 (27.8)	121.20±21.5	96-168
<b>Sex</b>			
Male	33 (91.7)		
Female	3 (8.3)		
P value	0.0001*		

\*Significant (P <0.001)

Of 36 patients, UTI was diagnosed in 14 (33.33%) patients based on significant colony count (5×10<sup>5</sup> ml/cfu) and the rest 22 (66.67%) were diagnosed by clinical signs and symptoms and pus cell count >5/HPF in urinalysis (Table 2).

**Table 2.** Diagnosis of UTI based on Urine culture and Urinalysis in study subjects (n=36)

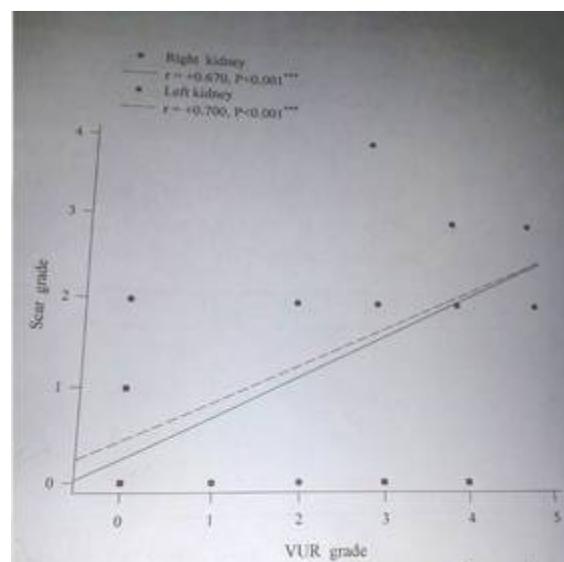
Parameters	Number	Percent (%)
Urine culture Colony count >10 <sup>5</sup> /ml	14	38.89
Urinalysis Pus cell >5/HPF	22	61.11

Micturiting cystourethrogram was performed in all patients; 19 (52.77%) patients had reflux. VUR was detected in 37(51.39%) renal units in patients evaluated for UTI. Mild reflux (grades I and II) was found in 2 (2.78%), moderate in 9 (12.5%) and severe in 26 (36.11%) cases (Table 3).

**Table 3.** MCUG findings and renal scars of the kidney units (n=72) in different age group in study cases

VUR grade	Age in month		
	<12 (n=14) Number (%)	12-60 (n=38) Number (%)	>60 (n=20) Number (%)
0	07 (50.0%)	16 (42.1)	10 (50.0)
I	00 (0.0)	01 (2.63)	00 (0.0)
II	00 (0.0)	01 (2.63)	00 (0.0)
III	02 (14.28)	04 (10.52)	03 (15.5)
IV	03 (21.42)	10 (26.3)	03 (15.5)
V	02 (14.28)	06 (15.78)	04 (20.0)

Of 36 children with documented UTI having 72 kidney units, 35 kidney units had normal cortical scintigraphy by DMSA scan and the rest 37 had scars in different grades both in the right and left kidneys. Grades I & II renal scar were found in 12 (33.33%) patients in the right kidney and 14 (38.88%) in the left kidney. Higher grades of scar (grades III & IV) were found in the right kidney and the left kidney as 5 (13.88%) and 6 (16.66%), respectively. In the present study, a positive correlation was found between grades of reflux and grades of renal scars. Higher grades of renal scars were directly co-related with higher grade of VUR (Fig 1) (for the right kidney r= +0.670, p<0.01; the left kidney r= +0.700, p<0.01).



**Figure 1.** Correlation of scar grade versus VUR grade

## Discussion

This study analyzed 36 children with UTI to determine the prevalence of VUR and renal scarring. The current study showed a male predominance (with a significant statistical difference,  $P$  value=0.001), which was contradictory to the widely known female predominance in UTI. The significant male preponderance in this study was probably due to the presence of complicated UTI, which is more prevalent in male child and also due to gender attention of parents towards the male child prevailing in our society. Most Chinese studies about UTI cases reported a male predominance, but some Chinese authors reported equal distribution of male and female patients with UTI [13-15]. Gorelick MH reported a higher proportion of complicated UTI like anatomical abnormalities, VUR and voiding dysfunction in male child than female ones [16].

There was a higher mean age of patients at presentation in this study population, which is probably due to unawareness or under-evaluation of previous UTIs. Higher rate of scars at presentation was also found, as incidence of renal scarring increases with each episode of pyelonephritis [17]. In this study, the severity of renal cortical scarring was proportionately increased in each episode of subsequent UTI.

The prevalence of VUR is not known in healthy children, however in UTI, the prevalence of VUR may vary from 29% to 50% [18]. In this study, 19 (52.77%) of 36 patients had different grades of reflux. Bhatnagar et al. from India found that 62% of children with UTI had VUR, of which a majority had grade V [19]. The similarity may be because both countries have similar geographical, cultural and social background and both studies were performed in tertiary level hospital where parents reach late. In a Chinese study, Yip et al. found 23% VUR in children presented with UTI, but in that study only two-third of children underwent MCUG.

In the present study, higher grade of VUR was found in older children. Thirty-eight percent of children in 12-60 month age group had reflux of high grade (grades III & IV). It is well known that reflux associated with UTI is more common in younger age group. In a study from USA, Chand et al. found the incidence of VUR as 52% in 0-2 years, 26% in 3-6 years, 18% in 7-11 years and 4% in 12-21 years. Lack of antenatal sonologic evaluation and late referral of patients are the two important risk factors for this occurrence [20].

The number of reflux is considerably high in UTI in this study. It is similar to the result of Orellana P et al. where VUR was detected in 43.49% of renal units with first and recurrent UTI, but higher than the study performed by Soylyu A, which showed 36.8%. The high incidence of reflux with advanced grade actually reflects late referral and parental ignorance and lack of proper knowledge. It also indicates under-diagnosis or inappropriate laboratory evaluation.

Biggie et al. reported that 80% kidneys with abnormal DMSA renal scan had higher grade of VUR (IV-V). In the current study, both kidneys with higher grade of reflux had linear positive correlation with higher grade of scar (for right kidney  $r = -0.484$ ,  $p < 0.01$ ; left kidney  $r = -0.424$ ,  $p < 0.01$ ). Therefore, observation of both studies was similar.

## Conclusion

In conclusion, predisposing factors of renal scarring among children presenting with UTI were male gender, younger age and high grade reflux and there is a positive correlation between renal scar and grade of reflux.

## Acknowledgement

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## Conflict of Interest

Authors had no conflict of interest.

## Financial Support

None declared

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**Results:** Of 36 patients, 33 (91.6%) were male and 3 (8.4%) female. Patients were divided into three groups based on their age (<12 months, 12-60 months and older than 60 months). VUR was detected in 37 (51.39%) renal units among all the group of patients evaluated for UTI. Mild reflux (grades I and II) was found in 2 (2.78%), moderate in 9 (12.5%) and severe in 26 (36.11%) patients. Of 72 kidney units, 37 kidney units had different grades of cortical scar. Grades I & II renal scar found in 12 (33.33%) patients in the right kidney and 14 (38.88%) in the left kidney. Higher grades of scar (grades III & IV) were found in the right kidney and the left kidney in 5 (13.88%) and 6 (16.66%) patients, respectively. A positive co-relation was observed between grades of reflux and grades of renal scars (for the right kidney  $r = +0.670$ ,  $p < 0.01$ ; the left kidney  $r = +0.700$ ,  $p < 0.01$ ).

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Renal scarring is associated with its fatal consequence like chronic kidney disease (CKD) in children. Children with higher grade of VUR have an increased likelihood of developing renal scarring [9]. The International reflux study reported that renal injury is more frequent in children less than two years with high grade VUR [10]. Therefore, evaluation of reflux and associated scarring is of paramount importance, particularly in younger age, who are more prone to develop such fatal consequences.

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>60	10 (27.8)	121.20±21.5	96-168
<b>Sex</b>			
<b>Male</b>	33 (91.7)		
<b>Female</b>	3 (8.3)		
<b>P value</b>	0.0001*		

\*Significant (P <0.001)

Of 36 patients, UTI was diagnosed in 14 (33.33%) patients based on significant colony count (5×10<sup>5</sup> ml/cfu) and the rest 22 (66.67%) were diagnosed by clinical signs and symptoms and pus cell count >5/HPF in urinalysis (Table 2).

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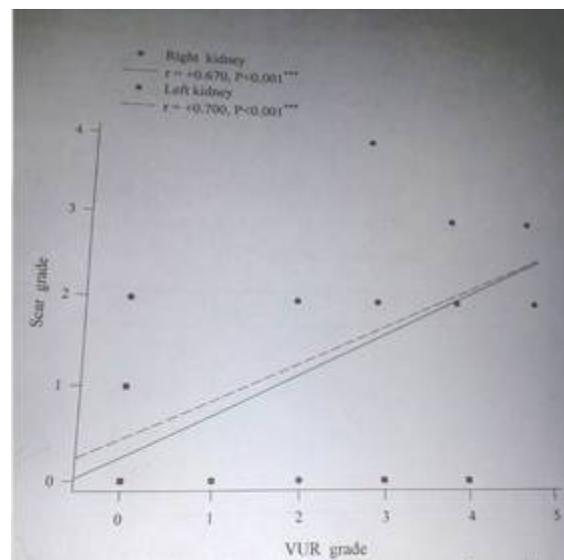
Parameters	Number	Percent (%)
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<b>Urinalysis Pus cell &gt;5/HPF</b>	22	61.11

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<b>I</b>	00 (0.0)	01 (2.63)	00 (0.0)
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<b>V</b>	02 (14.28)	06 (15.78)	04 (20.0)

Of 36 children with documented UTI having 72 kidney units, 35 kidney units had normal cortical scintigraphy by DMSA scan and the rest 37 had scars in different grades both in the right and left kidneys. Grades I & II renal scar were found in 12 (33.33%) patients in the right kidney and 14 (38.88%) in the left kidney. Higher grades of scar (grades III & IV) were found in the right kidney and the left kidney as 5 (13.88%) and 6 (16.66%), respectively. In the present study, a positive correlation was found between grades of reflux and grades of renal scars. Higher grades of renal scars were directly co-related with higher grade of VUR (Fig 1) (for the right kidney r= +0.670, p<0.01; the left kidney r= +0.700, p<0.01).



**Figure 1.** Correlation of scar grade versus VUR grade

## Discussion

This study analyzed 36 children with UTI to determine the prevalence of VUR and renal scarring. The current study showed a male predominance (with a significant statistical difference,  $P$  value=0.001), which was contradictory to the widely known female predominance in UTI. The significant male preponderance in this study was probably due to the presence of complicated UTI, which is more prevalent in male child and also due to gender attention of parents towards the male child prevailing in our society. Most Chinese studies about UTI cases reported a male predominance, but some Chinese authors reported equal distribution of male and female patients with UTI [13-15]. Gorelick MH reported a higher proportion of complicated UTI like anatomical abnormalities, VUR and voiding dysfunction in male child than female ones [16].

There was a higher mean age of patients at presentation in this study population, which is probably due to unawareness or under-evaluation of previous UTIs. Higher rate of scars at presentation was also found, as incidence of renal scarring increases with each episode of pyelonephritis [17]. In this study, the severity of renal cortical scarring was proportionately increased in each episode of subsequent UTI.

The prevalence of VUR is not known in healthy children, however in UTI, the prevalence of VUR may vary from 29% to 50% [18]. In this study, 19 (52.77%) of 36 patients had different grades of reflux. Bhatnagar et al. from India found that 62% of children with UTI had VUR, of which a majority had grade V [19]. The similarity may be because both countries have similar geographical, cultural and social background and both studies were performed in tertiary level hospital where parents reach late. In a Chinese study, Yip et al. found 23% VUR in children presented with UTI, but in that study only two-third of children underwent MCUG.

In the present study, higher grade of VUR was found in older children. Thirty-eight percent of children in 12-60 month age group had reflux of high grade (grades III & IV). It is well known that reflux associated with UTI is more common in younger age group. In a study from USA, Chand et al. found the incidence of VUR as 52% in 0-2 years, 26% in 3-6 years, 18% in 7-11 years and 4% in 12-21 years. Lack of antenatal sonologic evaluation and late referral of patients are the two important risk factors for this occurrence [20].

The number of reflux is considerably high in UTI in this study. It is similar to the result of Orellana P et al. where VUR was detected in 43.49% of renal units with first and recurrent UTI, but higher than the study performed by Soyly A, which showed 36.8%. The high incidence of reflux with advanced grade actually reflects late referral and parental ignorance and lack of proper knowledge. It also indicates under-diagnosis or inappropriate laboratory evaluation.

Biggie et al. reported that 80% kidneys with abnormal DMSA renal scan had higher grade of VUR (IV-V). In the current study, both kidneys with higher grade of reflux had linear positive correlation with higher grade of scar (for right kidney  $r = -0.484$ ,  $p < 0.01$ ; left kidney  $r = -0.424$ ,  $p < 0.01$ ). Therefore, observation of both studies was similar.

## Conclusion

In conclusion, predisposing factors of renal scarring among children presenting with UTI were male gender, younger age and high grade reflux and there is a positive correlation between renal scar and grade of reflux.

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## Conflict of Interest

Authors had no conflict of interest.

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