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Factors associated with renal scarring in children with vesicoureteral reflux

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ABSTRACT

Introduction: Vesicoureteral reflux (VUR), a prevalent urological disorder in pediatrics, often leads to severe consequences such as renal scarring, hypertension, and end-stage renal diseases.

Objectives: This study investigates the prevalence of renal scarring and its potential predisposing factors in children with VUR.

Patients and Methods: A prospective cross-sectional study was conducted at a pediatric tertiary referral hospital between 2014 and 2017. Patients diagnosed with VUR underwent TC99m-DMSA scans. The presence of a renal cortical uptake defect on the renal scan was indicative of renal scarring. In cases with a history of pyelonephritis, the persistence of renal cortical defects for ≥12 months following acute pyelonephritis was defined as renal scarring.

Results: A total of 93 patients were enrolled, comprising 62 girls (66.7%) and 31 boys (33.3%). The age of the initial visit to the nephrology clinic was 44.29 ± 43.38 months. Tc-99m DMSA scans identified renal scarring in 28 out of 93 (30.1%) patients and 41 out of 186 (22.04%) kidney ureter units (KUUs), encompassing 32 out of 111 (28.8%) refluxing and 9 out of 75 (12%) non-refluxing kidney units. Renal scarring was observed in 6 out of 21 (28.6%) cases with no history of urinary tract infection (UTI), 13 out of 57 (22.8%) cases with a history of pyelonephritis, and 9 out of 15 (60%) cases with a history of cystitis ($P=0.02$). Patients with renal scarring were diagnosed with VUR at an older age than those without scarring (45.38±37.37 versus 22.21±22.45 months, respectively; $P=0.0001$). The prevalence of renal scarring was 21.55% among cases seen in the nephrology clinic at or before the age of 5 years, whereas it was 50% among those referred after the age of 5 years ($P=0.006$). The diagnosis of VUR after age five years was significantly associated with renal scarring (61.5% versus 25%, respectively) ($P=0.003$). No significant associations were found between high-grade and mild-to-moderate VUR or between primary and secondary VUR with renal scarring ($P>0.05$ for both).

Conclusion: Renal scarring is prevalent in the VUR population, occurring as frequently in cases with a history of pyelonephritis as in those without. Early detection of VUR can potentially delay the development of renal scarring.

Implication for health policy/practice/research/medical education:
Vesicoureteral reflux is a common urological disorder frequently resulting in severe consequences, including renal scarring, hypertension, and end-stage renal diseases. The present study aims to elucidate the factors strongly linked to the development of renal scars within the pediatric population affected by vesicoureteral reflux.

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Introduction

Vesicoureteral reflux (VUR), the most prevalent urological anomaly in childhood, plays a significant role in initiating urinary tract infections (UTIs), renal parenchymal damage, and ultimately end-stage renal disease (1-6). Roughly 25%–40% of children experiencing their first episode of febrile UTI exhibit VUR (3). Renal scarring has been detected in 30%–49% of children diagnosed with

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VUR at the outset (6). Delayed or overlooked diagnosis and treatment of UTIs, recurrent UTIs, and high-grade VUR have been identified as important predisposing factors contributing to renal scarring (7-9). Although most investigations strongly support the connection between VUR and renal scarring, a minority of studies present contradictory findings (9,10).

Objectives

This current study aims to provide novel insights by describing the factors significantly associated with the formation of renal scars in the pediatric population affected by VUR.

Patients and Methods

Study design

A prospective cross-sectional study was conducted to ascertain the presence of renal scarring in patients diagnosed with VUR. The research took place in the nephrology clinic of a tertiary academic hospital from October 2014 to 2017. Technetium-99m (Tc-99m) dimercaptosuccinic acid (DMSA) scans were utilized for identifying renal scarring. Based on their history of UTI, patients were categorized into three groups:

Group 1 consisted of patients with no history of UTI, Group 2 included patients with a history of febrile UTI (pyelonephritis), and Group 3 comprised patients with a history of cystitis.

For patients in groups 1 and 3, Tc-99m-DMSA scans (renal scans) were recommended after diagnosing VUR. Patients with a history of pyelonephritis were advised to undergo a renal scan at least 4-6 months after a febrile UTI. A second renal scan was suggested in cases of recurring pyelonephritis or if kidney ultrasound findings indicated new scar development (such as a decrease in kidney size or renal cortical thickness or the identification of a new renal scar). Due to the study's location in a tertiary referral center, a subset of patients was referred several months (≥12 months) after experiencing acute pyelonephritis, with their initial renal scans obtained one year or more after the febrile UTI.

For patients in groups 1 and 3, the presence of a renal cortical uptake defect in the renal scan indicated renal scarring. In instances with a history of pyelonephritis (group 2), renal scarring was defined as the persistence of a renal cortical uptake defect for ≥12 months following the episode of pyelonephritis. Patients with pyelonephritis who underwent a renal scan < 12 months after a febrile UTI and exhibited a renal cortical uptake defect were included only if a second scan was conducted one year or more after the pyelonephritis (Figure 1).

Four grades for renal scars were considered "grade I,

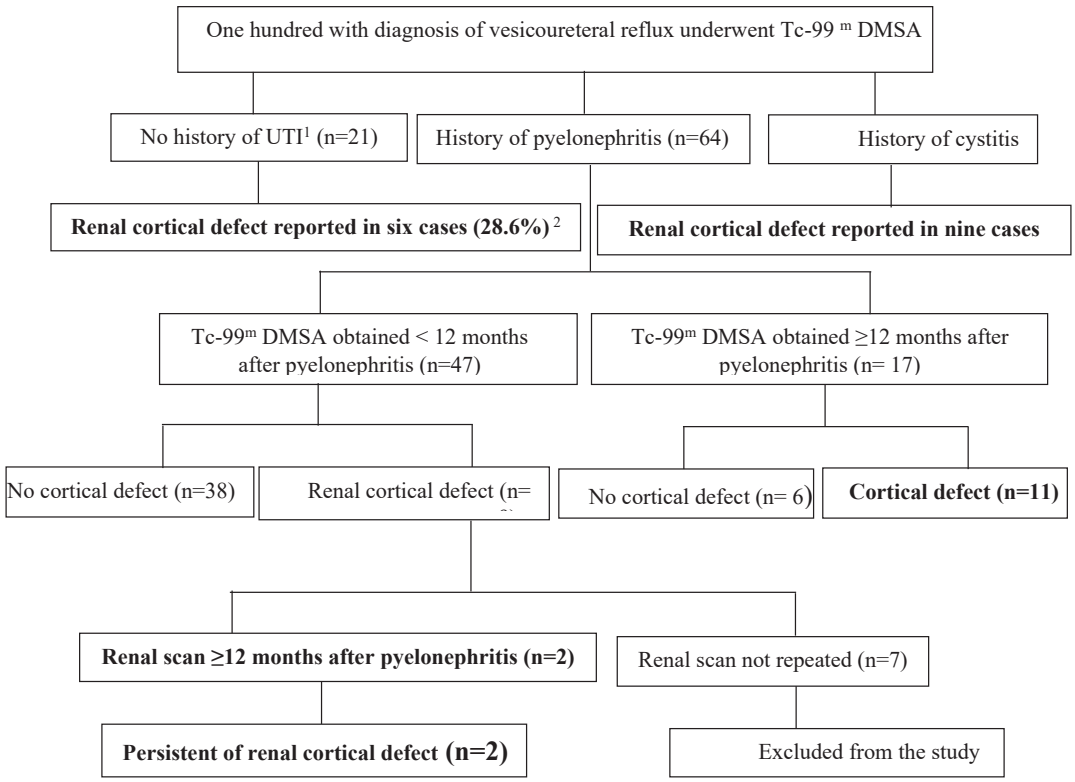

Figure 1. The method of evaluation of patients for renal scaring. UTI, Urinary tract infection. * Bolded parts define the patients with renal scar.

no more than two scarred areas; grade II, more than two scars with some areas of normal parenchyma between them; grade III, generalized damage to the whole kidney; grade IV, shrunken kidney with little or no uptake and differential renal function of <10% of the overall function"—grades III and IV of renal scars defined as severe scars (11).

The first outcome of the study was to define the frequency of renal scarring in the pediatric VUR population. The second outcome was to define any association of renal scarring with age at first UTI, age at the time of diagnosis of VUR and referring to nephrology clinic, gender, high grades VUR (grades IV and V) versus mild to moderate VUR (grades I-III), and primary versus secondary VUR.

Statistical analysis

Statistical analysis was conducted using SPSS software, version 16 (SPSS Institute, Inc, Chicago, IL, USA). All experimental values are presented as means ± standard deviation (SD) or frequencies. The normality of variables was assessed using the one-sample Kolmogorov-Smirnov test, and all variables demonstrated a normal distribution. Data analysis was performed using chi-square and independent t tests. A *P* value of less than 0.05 was considered statistically significant.

Results

Out of the initial 100 patients diagnosed with VUR, seven cases with a history of pyelonephritis were excluded from the study. These cases had undergone renal scans less than 12 months after pyelonephritis and displayed renal cortical uptake defects. However, they were excluded since the renal scans were not repeated one year or more after pyelonephritis to confirm the persistence of renal cortical uptake defects. Eventually, the study enrolled a total of 93 patients.

Among the enrolled cases, there were 62 girls (66.7%) and 31 boys (33.3%). The ages at their first visit to the nephrology clinic and the time of VUR diagnosis ranged from 5 days to 12 years and nine months (with a mean of 44.29 ± 43.38 months) and from 20 days to 11 years and eight months (with a mean of 29.26 ± 29.63 months), respectively. For patients with a history of UTI, the first infection occurred between the ages of 20 days and 11 years (with a mean of 25.52 ± 28.57 months). Table 1 outlines the VUR grades among the enrolled cases.

In total, VUR was observed in 111 out of 186 kidney ureter units (KUUs) (59.7%). This consisted of 54 out of 93 (58.06%) KUUs in the right kidney and 57 out of 93 (61.3%) in the left kidney. Bilateral VUR was identified in 18 out of 93 patients (19.35%). Considering the 75 (80.65%) cases with unilateral VUR, 75 out of 186 (40.3%) KUUs exhibited non-refluxing behavior. High-grade VUR was detected in 29 out of 93 (31.2%) cases and 39 out of 186 (21%) KUUs.

Table 1. Grading of VUR in enrolled cases

Grade of VUR	Patients No. (%)	Refluxing KUUs No. (%)
Grade I	5 (5.4)	6 (5.4)
Grade II	25 (26.9)	27 (24.32)
Grade III	35 (37.6)	43 (38.75)
Grade IV	13 (14)	17 (15.31)
Grade V	15 (16.1)	18 (16.22)
Total	93 (100)	111 (100)

VUR, Vesicoureteral reflux; KUUs, Kidney ureter units.

Ten patients (10.75%) had VUR secondary to either posterior urethral valve (PUV) (n = 4) or voiding dysfunction (n = 6). Among the 6 cases with voiding dysfunction, five (83.3%) were girls, and three cases (50%) displayed renal scarring. Two out of these three cases had severe and bilateral VUR. The diagnosis of voiding dysfunction was established based on a combination of factors, including the presence of lower urinary tract symptoms (such as daytime incontinence), bladder ultrasound findings (increased bladder wall thickness), voiding cystourethrogram findings (bladder diverticula, bladder neck widening), and urodynamic tests. Among the four boys with PUV, three of them (75%) had renal scarring, one had high-grade VUR, and all cases had unilateral VUR.

Age at the first UTI, age at the time of VUR diagnosis and referral to the nephrology clinic, high grades versus mild to moderate VUR, and primary versus secondary VUR showed no significant differences among patients with histories of pyelonephritis, cystitis, or no history of UTI ($P > 0.05$ for all). Male gender was significantly more common in patients with no history of UTI (76.2%) compared to cases with a history of pyelonephritis (22.8%) and those with cystitis (13.4%) ($P = 0.0001$; Table 2).

Renal scarring in refluxing and non-refluxing kidney units

Kidney ultrasound indicated findings suggest renal scarring in 12 out of 93 (12.9%) patients, including two cases without renal cortical defects in the TC99m-DMSA scan. These findings encompassed reduced cortical thickness, diminished renal size, and increased cortical echogenicity. Renal scarring was reported in 41 out of 186 (22.04%) KUUs, including 32 out of 111 (28.8%) refluxing and 9 out of 75 (12%) non-refluxing KUUs ($P = 0.014$; Table 3).

Renal scarring was significantly more prevalent in refluxing kidney units compared to non-refluxing units. Among the 75 patients with unilateral VUR, 20 (26.7%) had renal scarring, and among the 18 cases with

Table 2. Characteristics of patients based on history of urinary tract infection

Variable	No history of UTI (n=21); No. (%)	Pyelonephritis ± cystitis (n=57), No. (%)	Cystitis (n=15), No. (%)	*P* value[a]
Girl gender Boy gender	5 (23.8) 16 (76.2)	44 (77.2) 13 (22.8)	13 (86.6) 2 (13.4)	0.0001
High grades (IV & V) VUR Mild to moderate VUR	6 (28.6) 15 (71.4)	18 (31.6) 39 (68.4)	5 (33.3) 10 (66.7)	0.95
Primary VUR Secondary VUR	21 (100) 0(0)	49 (86) 8 (14)	14 (93.3) 1 (6.7)	0.174
Age at the first clinic visit ≤ 2 years Age at the first clinic visit >2 years	15 (71.4) 6 (28.6)	21(36.8) 36 (63.2)	5 (33.3) 10 (66.7)	0.016
Age at first UTI ≤ 2 years Age at first UTI > 2 years	- -	36 (63.15 21 (36.85)	8 (53.3) 7 (46.7)	0.657
Age at the VUR diagnosis ≤ 2 years Age at the VUR diagnosis > 2 years	17 (81) 4 (19)	30 (52.6) 27 (47.4)	8 (53.3) 7 (46.7)	0.657
Age at the first clinic visit ≤ 5 years Age at the first clinic visit > 5 years	18 (85.7) 3 (14.3)	38 (66.7) 19 (33.3)	9 (60) 6 (40)	0.176
Age at first UTI ≤ 5 years Age at first UTI > 5 years	- -	50 (87.7) 7 (12.3)	11 (3.3) 4 (26.7)	0.124
Age at the VUR diagnosis ≤ 5 Age at the VUR diagnosis > 5	19 (90.5) 2 (9.5)	50 (87.7) 7 (12.3)	11 (73.3) 4 (26.7)	0.229

UTI, Urinary tract infection; VUR, vesicoureteral reflux.
[a] Chi square or Fisher exact tests. Fisher exact test was used for comparing age at first UTI ≤ 5 years versus > 5 years.

Table 3. Renal scar in unilateral versus bilateral VUR

Variable	Patients with Unilateral VUR (KUUs=150); No. (%)	Patients with bilateral VUR (KUUs =36); No. (%)	Total KUUs; (n=186); N (%)
No scar (KUUs)	129 (86)	16 (44.45)	145 (77.96)
Scar in refluxing KUUs	8 (5.33)	-	32(17.21)
Scar in non-refluxing KUUs	5 (3.34)	-	9 (4.83)
Bilateral scar (KUUs)	8 (5.33)[a]	4 (11.1)	12(6.45)
Unilateral scar (KUUs)	13 (8.66)[b]	16 (44.45)	29 (15.6)

VUR, vesicoureteral reflux; KUUs, Kidney ureter units.
[a] It includes four non-refluxing KUUs. [b] It includes scars in refluxing and non–refluxing kidney ureter units of systems with unilateral VUR.

bilateral VUR, 8 (44.4%) had renal scarring (*P*=0.14). Furthermore, 2 out of 18 (11.1%) patients with bilateral VUR had bilateral renal scars. Severe renal scarring (renal scar grades III & IV) was identified in 10 out of 186 (5.4%) kidney units (see Table 4).

Frequency of renal scarring based on history of UTI

Tc-99m DMSA scans revealed renal scarring in 28 out of 93 (30.1%) patients, including 6 out of 21 (28.6%) cases with no history of UTI, 13 out of 57 (22.8%) with a history of pyelonephritis, and 9 out of 15 (60%) with a history of cystitis (*P*=0.02). Among cases with no history of UTI, 18 (85.7%) patients had unilateral VUR. Renal scarring was reported in 4 out of 18 (22.2%) cases and 5 out of 36 (13.9%) KUUs, including 3 out of 18 (16.7%) refluxing and 2 out of 18 (11.1%) non-refluxing KUUs (*P*=0.63). Among patients with a history of pyelonephritis (group 2, n=57), 45 (78.9%) had unilateral VUR. Renal scarring was observed in 7 out of 45 (15.5%) patients and 9 out of 90 (10%) KUUs. This included 4 out of 45 (8.9%) refluxing and 5 out of 45 (11.1%) non-refluxing KUUs (*P*=0.725). In group 3 (patients with a history of cystitis, n=15), 12 cases (80%) had unilateral VUR. Renal scarring was identified in 7 out of 24 (29.1%) KUUs, encompassing 5 out of 12 (41.7%) refluxing and 2 out of 12 (16.7%) non-refluxing KUUs (*P*=0.178).

Demographic characteristics, grading, and types (primary versus secondary) of VUR were compared between patients with and without renal scarring (see Table 5). Patients with renal scarring were older at the time of VUR diagnosis than those without (45.38±37.37 versus 22.21±22.45 months, respectively; *P*=0.0001). Renal scarring was observed in 21.55% and 50% of patients who visited the nephrology clinic at ≤5 and >5 years, respectively (*P*=0.006). Furthermore, renal scarring was significantly more common in patients diagnosed with VUR after five years compared to those diagnosed before or at the age of 5 years (61.5% versus 25%, respectively;

Table 4. Grading of renal scar in patients

Grading of renal scar	Kidney ureter units; N (%)
No scar	145 (77.95)
Grade I[a]	19 (10.21)
Grade II[b]	9(4.84)
Grade III[c]	8 (4.3)
Grade IV[d]	2(1.07)
Total	186 (100)[e]

[a] No more than two scarred; [b] More than two scars with some areas of normal parenchyma between them; [c] Generalized damage to the whole kidney, diffuse cortical defects with or without normal parenchyma between scars; [d] Shrunken kidney with little or no uptake of DMSA, i.e., <10% of the overall function; [e] Grading of renal scar was not clear in three KUUs.

$P=0.003$). Interestingly, renal scarring was equally prevalent in patients with high-grade VUR and those with mild to moderate VUR (31% versus 29.7%, respectively, $P=0.897$). Additionally, gender, types of VUR (primary versus secondary), and age at the first UTI showed no significant differences between the two groups (P>0.05 for all; Table 5).

Renal scarring in high-grade versus mild to moderate VUR

High-grade VUR was identified in 29 out of 93 (31.2%) patients and 39 out of 186 (21%) KUUs. Among the total patients, 10.75% had bilateral high-grade VUR. Out of the 39 KUUs affected by high-grade VUR, renal scarring was noted in 11 (28.2%) kidney units. Mild to moderate VUR (grades I-III) were found in 64 out of 93 (68.8%) patients and 72 out of 186 (38.7%) KUUs. Among these, 8 patients (8.6%) exhibited bilateral VUR grades I-III. Renal scarring was observed in 21 out of 72 (29.1%) KUUs affected by mild to moderate VUR. The prevalence of renal scarring was comparable between high-grade and mild to moderate VUR (28.2% compared to 29.1%, respectively; $P=0.766$).

Moreover, among the total patients, 75 out of 93 (80.6%) had unilateral VUR, indicating the absence of VUR in 75 out of 186 (40.3%) KUUs. Renal scans revealed scarring in 9 out of 75 (12%) non-refluxing KUUs. The prevalence of renal scarring was significantly lower in non-refluxing KUUs compared to those with high-grade and mild to moderate VUR (12% versus 28.2% and 29.1%, respectively; $P=0.017$).

Renal scarring in primary versus secondary VUR

Bilateral VUR was identified in 16 out of 83 (19.3%) patients with primary VUR and 2 out of 10 (20%) patients with secondary VUR. Among the patients with secondary VUR (n=10), 12 out of 20 (60%) KUUs exhibited no renal scarring. Of eight KUUs affected by renal scarring, three (37.5%) were non-refluxing units. In cases of primary VUR (n=83), renal scarring was observed in 27 out of 99 (27.3%) refluxing and 6 out of

Table 5. Characteristics of patients with versus those without renal scarring

Variable	Renal scar (n=28)	No renal scar (n=65)	*P* value
Age at the first clinic visit (month)	59.42±41.53	37.77±42.83	0.026[a]
Age at first episode of UTI (month)	32.9±39.93	22.22±21.44	0.156[a]
Age at the VUR diagnosis (month)	45.38±37.37	22.21±22.45	0.0001[a]
Variable	**Renal scar; No. (%)**	**No renal scar; No. (%)**	***P* value**
Age ≤2 years at VUR diagnosis Age >2 years at VUR diagnosis	11(20) 17 (44.75)	44 (80) 21 (55.25)	0.012[b]
Age ≤5 years at VUR diagnosis Age >5 years at VUR diagnosis	20 (25) 8 (61.5)	60 (75) 5 (38.5)	0.003[b]
Age ≤2 years at the first visit Age >2 years at the first visit	9 (21.95) 19 (36.55)	32 (78.05) 33 (63.45)	0.128[b]
Age ≤5 years at the first visit Age >5 years at the first visit	14 (21.55) 14(50)	51 (78.45) 14(50)	0.006[b]
Age at the first UTI ≤ 5 years[c] Age at the first UTI > 5 years	17 (27.9) 4 (57.1)	44 (72.1) 3 (42.9)	0.112[b]
Age ≤2 years[c] at first UTI) Age >2 years at first UTI	13 (29.55) 8 (33.3)	31 (70.45) 16 (66.7)	0.723[b]
High grades VUR [d] Mild to moderate VUR	9 (31) 19 (29.7)	20 (69) 45 (70.3)	0.896[b]
Primary VUR Secondary VUR	21(25.3) 6(60)	62 (74.7) 4 (40)	0.024[a]
Girl gender Boy gender	21(33.9) 7 (22.6)	41(66.1) 24 (77.4)	0.263[b]

UTI, Urinary tract infection; VUR, Vesicoureteral reflux.
[a] Independent t test; [b] Chi square test; [c] 21 patients had no history of UTI and the age at first UTI was not determined in 4 patients; [d] VUR grades IV & V.

67 (9%) non-refluxing KUUs. In total, renal scarring was identified in 33 out of 166 (19.9%) KUUs with primary VUR and 8 out of 20 (40%) kidney units with secondary VUR ($P=0.04$).

Severe renal scarring

Renal scans for patients with high-grade VUR revealed renal scar grades I-IV in 6, 1, 3, and 1 KUUs, respectively. This indicated that 4 out of 39 (10.25%) KUUs affected by high-grade VUR displayed severe renal scarring, signifying severe renal parenchymal damage. For patients with mild to moderate VUR, TC99m-DMSA scans revealed renal scarring grades I-IV in 11, 5, 5, and zero KUUs, respectively. Therefore, 5 out of 72 (6.9%) KUUs affected by mild to moderate VUR exhibited severe renal scarring. The prevalence of severe renal scarring was comparable between KUUs with high-grade and mild to moderate VUR (10.25% compared to 6.9%, respectively; $P=0.542$).

Discussion

Renal cortical scintigraphy using a Tc-99m-DMSA scan is the gold standard imaging method for diagnosing renal scarring (12). The presence of regional cortical uptake defects can be observed during acute pyelonephritis and can subsequently lead to permanent scarring (13). Among children affected by pyelonephritis, renal scars have been found in 40% and 6% of cases with and without VUR, respectively ($P=0.0001$) (7).

A study by Lee et al (8) investigated renal scar formation in children with unilateral primary VUR. The diagnosis of VUR was established following an imaging study for the first pyelonephritis episode. DMSA scans were performed within three days after the febrile UTI episode, with a second scan conducted six months after acute pyelonephritis. Renal defects were reported in 70.8% of refluxing and 27.1% of non-refluxing rental units, respectively ($P<0.01$, OR: 6.54). The second scan revealed renal scarring in 47.9% of refluxing and 14.6% of non-refluxing rental units, respectively ($P<0.01$, OR: 5.39). Their findings confirmed that VUR poses a risk factor for post-pyelonephritic renal scarring in children. They also noted that the prevalence of renal scars did not significantly differ based on the grade of VUR. In our current study, 45 out of 75 cases (60%) with unilateral VUR had a history of pyelonephritis. We observed renal scarring in 3/45(4.4%) refluxing and 4/45(6.6%) non-refluxing KUUs, respectively ($P=0.694$).

Another study suggested that around 20% of children with VUR experience renal scarring (14). In our study, which included 93 pediatric patients with VUR, we found a prevalence rate of 30.1% for renal scarring. It's important to differentiate between renal scarring and acute pyelonephritis, as both conditions can lead to renal cortical uptake defects on scans. Permanent renal cortical defects characterize renal scars, while uptake defects due to pyelonephritis tend to be transient.

In a different study, Aboutaleb and colleagues examined the association between VUR grade, UTI, and renal scarring (15). They categorized patients into three groups based on presentation: afebrile UTI, febrile UTI, and prenatal hydronephrosis. Enrolling 150 patients with 194 refluxing KUUs, they followed them for an average of 45 months. Renal scarring was observed in 46.7% of patients and 48.4% of KUUs. The scar group's presentation included febrile UTI (65.7%), afebrile UTI (20%), and prenatal hydronephrosis (14.3%). They concluded that higher VUR grades and UTI are associated with renal scarring, recommending early evaluation of VUR in infants, regardless of febrile UTI.

In our study, we reported renal scarring in 28 cases (30.1%), with 46.4% of cases presenting with febrile UTI, 32.1% with afebrile UTI, and 21.5% with presentations other than UTI. Renal scarring was detected in 24 (58.5%), 10 (24.4%), and 7 KUUs (17.1%) for patients with a history of febrile UTI, afebrile UTI, and no UTI history, respectively.

The frequency of renal scarring in our study was lower than the one reported by Aboutaleb and colleagues (30.1% compared to 46.7%, respectively). This difference may be attributed to the optimal time for diagnosing renal scarring. They considered an interval of ≥6 months for performing renal scans, whereas in our study, it was ≥12 months for patients with a history of febrile UTI. We excluded seven patients with febrile UTI with an abnormal renal scan performed less than 12 months after infection.

A study examined the changes in renal scans in children under five years old after their first acute pyelonephritis. The renal scans were conducted at 2-6 months, 6 months, and 2 years after febrile UTI. The first scan revealed renal cortical defects in 22/50 (44%) cases. The second renal scan showed persistent defects in 24% of patients. The third renal scan demonstrated the resolution of renal cortical defects in 47% of kidneys. The study revealed that during acute pyelonephritis, uptake defects were detectable in 34-70% of patients, which persisted in 9.5-38% of cases during follow-up (6).

In our study, the renal scans were performed at different intervals after acute pyelonephritis. First renal scans were conducted 4-6 and 7-11 months after acute pyelonephritis, revealing uptake defects in 2/12 (16.7%) and 2/3 (66.7%) cases, respectively. A subset of patients was referred one year or more after acute pyelonephritis. For these cases, renal scans were conducted for 1-2 years (n=8) and over two years (n=9) after febrile UTI. Renal cortical uptake

defects were found in 2/8 (25%) and 3/9 (33.3%) patients. Among nine cases whose renal scans were obtained within one year after pyelonephritis and reported renal cortical defects, two (22.2%) patients underwent a second renal scan. Both cases showed persistent uptake defects. The second scan was performed 14 months and 4.5 years after febrile UTI. Hoberman et al (6) reported findings consistent with acute pyelonephritis in renal scans obtained 48 hours after febrile UTI in 190/309 (61.5%) infants aged 1 to 24 months. The second scan, conducted six months after pyelonephritis, revealed renal cortical uptake defects in 26/275 (9.5%) patients. In our cases, the renal scan performed 6 months after acute pyelonephritis reported renal scarring in one out of five patients (20%).

The resolution of defects can take up to 6 months following the episode of acute pyelonephritis (16,17). Wallin and colleagues (17) examined Tc-99m DMSA findings in children with febrile UTI in the acute stage of pyelonephritis after six months and one year later. During the acute stage, parenchymal defects were found in all cases. After six months, the defects diminished or disappeared in 66% of the kidneys. However, the renal scan did not show improvement in renal cortical defects at one year. Inflammatory lesions from UTI may not resolve completely within six months of the infection. Ditchfield et al (16) discovered that 47% of defects in renal scans completely resolved 23-26 months after the first episode of febrile UTI.

Our study identified renal cortical uptake defects in eleven out of seventeen (64.7%) patients who underwent renal scans ≥12 months after acute pyelonephritis. The optimal time for performing a renal scan to distinguish acute pyelonephritis from renal scarring is variable, but an interval of at least six months is suggested. Renewal scarring should be considered if renal defects persist after six months (18). We found that older age at the time of VUR diagnosis, a visit to the nephrology clinic, and a VUR diagnosis after the age of 5 years were significantly associated with renal scarring ($P=0.0001$, 0.006, and 0.003, respectively). Although some studies (19,20) revealed a clear relationship between renal scarring, the type of UTI (febrile or non-febrile), and the grade of VUR, our results contradicted these associations. Novak et al (21) reported renal scarring in 64% of children aged 1-36 months with UTI. In our series, 41/57 (71.9%) patients with a history of acute pyelonephritis were aged 1-36 months during their first febrile UTI episode. Renal scarring was determined in 10 (24.4%) cases during follow-up. They also reported a strong link between the risk of renal scarring and the mean age at the first clinic visit and VUR diagnosis ($P=0.003$ and 0.01, respectively), consistent with our results.

Another study reported renal scarring in 64% of children aged 1-18 years with UTI and VUR (22). Snodgrass et al (20) examined a broader group of patients with UTI and found that high-grade VUR, recurrent UTI, and older age could significantly increase the risk of renal scarring. In our study, which included patients with VUR with or without a history of UTI, the occurrence of renal scarring did not significantly differ between KUUs with high-grade and mild to moderate VUR (28.2% compared to 29.1%, $P=0.766$). Among cases with a history of pyelonephritis (n=57), renal scarring was found in 4/18 (22.2%) and 9/39 (23.07%) patients with high-grade and mild to moderate VUR, respectively ($P=0.943$).

It has been suggested that in primary VUR, age and gender are not significant risk factors for the development of renal scarring. At the same time, recurrent UTIs (≥3) and VUR severity are significant risk factors (19). We did not find any significant association between high-grade VUR and renal scarring. However, older age at the time of VUR diagnosis, visiting the nephrology clinic, and VUR diagnosis after age five years were significantly associated with renal scarring ($P<0.05$ for all). We did not evaluate the impact of the number of febrile UTIs on the development of renal scarring because renal scans were conducted in most cases after the first febrile UTI.

Children with low-grade VUR (grades I-III) have a four times higher risk of developing renal scarring than those with non-refluxing units (23). In our series, 21/72 (29.1%) refluxing (low-grade VUR; grades I-III) and 9/75 (12%) non-refluxing kidney units were affected by renal scarring ($P=0.01$). In a multicenter, randomized, placebo-controlled trial involving 607 children aged 2-71 months, all with VUR grades I-IV, renal scarring was found to be significantly more common in relatively older children and those with a second episode of febrile or symptomatic UTI before enrollment in the study. Additionally, renal scarring (before and after randomization) was significantly noted in KUUs with high-grade VUR (grade IV) compared to those with low-grade or non-refluxing KUUs (24). Similar to this study, in our series, patients with renal scarring were significantly older at the first clinic visit and at the time of VUR diagnosis than those without renal scarring ($P=0.026$ and 0.0001, respectively). Furthermore, renal scarring was more prevalent in refluxing versus non-refluxing KUUs (28.8 compared to 12%, respectively, $P=0.014$).

Conclusion

This study unequivocally establishes that early diagnosis of VUR (before age five years) with the implementation of preventative measures to reduce UTIs can decrease or delay the development of renal scarring in the pediatric VUR population. The grade of VUR (high-grade versus mild to moderate VUR) does not appear to be a significant

factor in the development of renal scarring. It is important to note that patients with a history of febrile UTI have the same likelihood of renal scarring as those without such a history.

Limitations of the study

We did not evaluate the impact of some febrile UTIs on the development of renal scarring. In addition, the low number of patients with secondary VUR was a limitation for comparing renal scarring in patients with primary versus secondary VUR. The main advantage of the current study is that it represents the VUR population with and without a history of acute pyelonephritis. As a result, it compares the prevalence of renal scarring in different groups of the VUR population.

Authors' contribution

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Ethical issues

The research conducted in this study adhered to the principles outlined in the Declaration of Helsinki and was approved by the Ethics Committee of Mashhad University of Medical Sciences approved this study. The institutional ethical committee at Mashhad University of Medical Sciences approved all study protocols (Ethical code# IR.MUMS.fm.REC.1394.589) . Prior to any intervention, all participants provided written informed consent. This study extracted from M.D thesis of Seyyedeh Fatemeh Ghalibafan at this university (Thesis# 941070). The authors have fully complied with ethical issues, such as plagiarism, data fabrication, and double publication.

Conflicts of interest

The authors declare that there is no conflict of interest.

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References

1. Cheng CH, Tsai MH, Huang YC, Su LH, Tsau YK, Lin CJ, et al. Antibiotic resistance patterns of community-acquired urinary tract infections in children with vesicoureteral reflux receiving prophylactic antibiotic therapy. Pediatrics. 2008;122:1212-7. doi: 10.1542/peds.2007-2926.
2. Thakre AA, Sreedhar B, Yeung CK. Laparoscopy in the management of pediatric vesicoureteral reflux. Indian J Urol. 2007;23:414-9. doi: 10.4103/0970-1591.36716.
3. Cleper R, Krause I, Eisenstein B, Davidovits M. Prevalence of vesicoureteral reflux in neonatal urinary tract infection. Clin Pediatr (Phila). 2004;43:619-25. doi: 10.1177/000992280404300706.
4. Kakizaki H, Moriya K, Ameda K, Shibata T, Tanaka H, Koyanagi T. Diameter of the external urethral sphincter as a predictor of detrusor-sphincter incoordination in children: comparative study of voiding cystourethrography. J Urol. 2003;169:655-8. doi: 10.1097/01.ju.0000040664.33499.ba.
5. Homayoon K, Chen JJ, Cummings JM, Steinhardt GF. Voiding dysfunction: outcome in infants with congenital vesicoureteral reflux. Urology. 2005;66:1091-4. doi: 10.1016/j.urology.2005.05.053.
6. Hoberman A, Charron M, Hickey RW, Baskin M, Kearney DH, Wald ER. Imaging studies after a first febrile urinary tract infection in young children. N Engl J Med. 2003;348:195-202. doi: 10.1056/NEJMoa021698.
7. Polito C, Rambaldi PF, Signoriello G, Mansi L, La Manna A. Permanent renal parenchymal defects after febrile UTI are closely associated with vesicoureteric reflux. Pediatr Nephrol. 2006;21:521-6. doi: 10.1007/s00467-006-0036-3.
8. Lee JH, Son CH, Lee MS, Park YS. Vesicoureteral reflux increases the risk of renal scars: a study of unilateral reflux. Pediatr Nephrol. 2006;21:1281-4. doi: 10.1007/s00467-006-0147-x.
9. Garin EH, Olavarria F, Garcia Nieto V, Valenciano B, Campos A, Young L. Clinical significance of primary vesicoureteral reflux and urinary antibiotic prophylaxis after acute pyelonephritis: a multicenter, randomized, controlled study. Pediatrics. 2006;117:626-32. doi: 10.1542/peds.2005-1362.
10. Doganis D, Siafas K, Mavrikou M, Issaris G, Martirosova A, Perperidis G, et al. Does early treatment of urinary tract infection prevent renal damage? Pediatrics. 2007;120:e922-8. doi: 10.1542/peds.2006-2417.
11. Goldraich NP, Ramos OL, Goldraich IH. Urography versus DMSA scan in children with vesicoureteric reflux. Pediatr Nephrol. 1989;3:1-5. doi: 10.1007/bf00859614.
12. Rabie Saleh Farghaly H, Mohamed Sayed MH. Technetium-99m dimercaptosuccinic acid scan in evaluation of renal cortical scarring: is it mandatory to do single photon emission computerized tomography? Indian J Nucl Med. 2015;30:26-

30. doi: 10.4103/0972-3919.147530.
13. Piepsz A. Radionuclide studies in paediatric nephro-urology. Eur J Radiol. 2002;43:146-53. doi: 10.1016/s0720-048x(02)00111-0.
14. Lim R. Vesicoureteral reflux and urinary tract infection: evolving practices and current controversies in pediatric imaging. AJR Am J Roentgenol. 2009;192:1197-208. doi: 10.2214/ajr.08.2187.
15. Aboutaleb H, Abouelgreed TA, El-Hagrasi H, Bakry Eldib D, Abdelaal MA, El Gohary MA. Correlation of renal scarring to urinary tract infections and vesicoureteral reflux in children. Adv Urol. 2022;2022:9697931. doi: 10.1155/2022/9697931.
16. Ditchfield MR, Summerville D, Grimwood K, Cook DJ, Powell HR, Sloane R, et al. Time course of transient cortical scintigraphic defects associated with acute pyelonephritis. Pediatr Radiol. 2002;32:849-52. doi: 10.1007/s00247-002-0784-6.
17. Wallin L, Helin I, Bajc M. Follow-up of acute pyelonephritis in children by Tc-99m DMSA scintigraphy: quantitative and qualitative assessment. Clin Nucl Med. 2001;26:423-32. doi: 10.1097/00003072-200105000-00010.
18. Stokland E, Hellström M, Jakobsson B, Sixt R. Imaging of renal scarring. Acta Paediatr Suppl. 1999;88:13-21. doi: 10.1111/j.1651-2227.1999.tb01314.x.
19. Mir S, Ertan P, Ozkayin N. Risk factors for renal scarring in children with primary vesicoureteral reflux disease. Saudi J Kidney Dis Transpl. 2013;24(1):54-9. doi: 10.4103/1319-2442.106241.
20. Snodgrass WT, Shah A, Yang M, Kwon J, Villanueva C, Traylor J, et al. Prevalence and risk factors for renal scars in children with febrile UTI and/or VUR: a cross-sectional observational study of 565 consecutive patients. J Pediatr Urol. 2013;9(6 Pt A):856-63. doi: 10.1016/j.jpurol.2012.11.019.
21. Novak TE, Mathews R, Martz K, Neu A. Progression of chronic kidney disease in children with vesicoureteral reflux: the North American Pediatric Renal Trials Collaborative Studies Database. J Urol. 2009;182(4 Suppl):1678-81. doi: 10.1016/j.juro.2009.02.085.
22. 22. Zajaczkowska M, Zinkiewicz Z, Duda B, Kołacz A, Szajner-Milart I. [Anatomic and functional disorders of the urinary tract in children with urinary tract infections]. Pol Merkur Lekarski. 2001;10(58):213-5. [Polish].
23. 23. Zaffanello M, Franchini M, Brugnara M, Fanos V. Evaluating kidney damage from vesico-ureteral reflux in children. Saudi J Kidney Dis Transpl. 2009;20:57-68.
24. 24. Mattoo TK, Chesney RW, Greenfield SP, Hoberman A, Keren R, Mathews R, et al. Renal scarring in the randomized intervention for children with vesicoureteral reflux (RIVUR) trial. Clin J Am Soc Nephrol. 2016;11:54-61. doi: 10.2215/cjn.05210515.