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ORIGINAL RESEARCH

Vesicoureteral Reflux in Children with Urinary Tract Infections in the Inpatient Setting in Taiwan

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Purpose: Children with vesicoureteral reflux (VUR) are at an increased risk of recurrent urinary tract infections (UTIs). Early detection and treatment of VUR are important to prevent renal function impairment. Therefore, the aims of this study were to determine the epidemiology of VUR and to identify clinical factors associated with VUR in Taiwanese children with a first documented UTI.

Patients and Methods: We conducted this nationwide retrospective study using the Longitudinal Health Insurance Database 2010. Children ≤6 years of age who were admitted and received intravenous antibiotics for a newly diagnosed UTI were included. Multivariate logistic regression analysis was used to identify independent factors associated with VUR.

Results: Overall, 388 (10.2%) of the children had VUR. The median (interquartile range) age at diagnosis of VUR was 0.5 (0.3–1.3) years. Among the children with VUR, the age at first UTI and the age at diagnosis of VUR were significant lower in the males than in the females. Age ≤1 year at the first UTI (odds ratio (OR), 1.3; 95% confidence interval (CI): 1.0–1.7), renal agenesis and dysgenesis (OR, 4.1; 95% CI: 1.3–13.1), hydronephrosis (OR, 2.2; 95% CI: 1.7–2.9), duplex collecting system/ectopic kidney/ectopic ureter (OR, 13.0; 95% CI: 8.1–20.8), neuropathic bladder (OR, 4.7; 95% CI: 2.0–11.1) and spina bifida (OR, 5.9; 95% CI: 1.3–27.8) were independent factors for VUR.

Conclusion: The children with VUR were more likely to have small kidneys and progression to end-stage renal disease. VUR was common in the children with a UTI and who were ≤1 year of age. Clinicians should arrange ultrasound to diagnose urinary tract anomalies. Infants with urinary tract anomalies, neuropathic bladder and spina bifida should receive further voiding cystourethrography to diagnose VUR early, as this may help to prevent renal damage.

Keywords: congenital anomalies of the kidney and the urinary tract, vesicoureteral reflux, urinary tract infection, risk factor

Introduction

Primary vesicoureteral reflux (VUR) is a common congenital urinary tract anomaly characterized by retrograde flow of urine from the bladder to the kidneys. The prevalence of VUR has been reported to range from 0.4–2% in the general population.[1,2] Most reflux is discovered during an initial evaluation for urinary tract infections (UTIs). However, the prevalence of VUR in children with UTIs varies among different racial and patient groups. VUR has been reported in up to 10–51.4% of children being investigated for a first UTI, with the lowest prevalence in black children.[3–8]

At the time of diagnosis, 30–54% of children with VUR have been reported to have renal parenchymal scarring.[9–12] In addition, the severity of VUR in black patients has been reported to be significantly lower than in white girls.[13] High-grade VUR and repeated pyelonephritis are considered to be the most important risk factors for renal scar development in children.[14–16] In addition, sex differences have been reported in the development of renal parenchymal damage, with boys tending to present antenatally or during the first year of life and often with bilateral severe VUR.[17] Girls are usually first diagnosed at an older age, and their VUR is often less severe and prone to recurrent UTIs.

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Prior reports have demonstrated a lower UTI rate in circumcised boys. The low prevalence of circumcision among Taiwanese boys and the adequate prenatal examinations of pregnant women provided by the National Health Insurance (NHI) system in Taiwan may influence the epidemiology of VUR with regards to UTIs. Identifying children with UTIs who are at a high potential risk of VUR at an early age is critical to decrease renal damage and associated long-term complications. Moreover, the need for voiding cystourethrogram (VCUG) after a first febrile UTI in children is uncertain. Therefore, we conducted this population-based cohort study to evaluate the epidemiology of VUR and other genitourinary tract anomalies in Taiwanese children hospitalized for acute pyelonephritis to investigate sex-specific differences and determine the clinical factors associated with VUR.

Materials and Methods

Data Source

Over 99.9% of the population in Taiwan are covered by the NHI program. The Taiwan National Health Insurance Research Database (NHIRD) contains all records of both outpatient and inpatient claims data of nearly the entire Taiwanese population. In this study, we used a subset of the NHIRD, the Longitudinal Health Insurance Database 2010 (LHID 2010). The LHID 2010 includes the entire medical claims data of one million beneficiaries randomly sampled from the registry of beneficiaries in the NHIRD. All individually identifiable health information is deidentified and encrypted before data are released for use in research. This study was approved by the Institutional Review Board of Taipei Veterans General Hospital (2017-07-016AC), which waived the need for informed consent.

Study Population and Case Ascertainment

We selected children ≤ 6 years of age who were hospitalized with a newly diagnosed UTI (International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) 771.82, 599.0, 590.1, 590.2, 590.3, 590.8, 590.9) from the LHID 2010 from 1998 to 2013. To further assure the validity of the diagnosis of a UTI, only patients diagnosed with a UTI who received intravenous antibiotics (anatomical therapeutic chemical (ATC) codes: J01A, J01B, J01C, J01D, J01E, J01G, J01M and J01X) or oral sulfonamides and trimethoprim (ATC code: J01E) during the hospitalization were considered to be new cases of UTI. The exclusion criteria were: (1) cases who had a urine culture but did not do it in conjunction with susceptibility testing indicating negative urine culture results; (2) a concurrent diagnosis of acute cystitis (ICD-9-CM 595.0); and (3) a history of VUR before the index date. The study population was divided into two subgroups: those ≤ 1 year (infant) of age, and those > 1 year of age. The patients were followed until December 31, 2013.

VUR, Other Congenital Renal and Urologic Anomalies and Comorbidities

Children with a new diagnosis code for VUR (ICD-9-CM 593.7x, 593.70, 593.71, 593.72, 593.73) during the follow-up period were defined as having VUR in this study. We also investigated the following congenital anomalies of the kidney and urinary tract (CAKUT): renal agenesis and dysgenesis (ICD-9-CM 753.0); cystic kidney disease (ICD-9-CM 753.1); obstructive defects of the renal pelvis and ureter (ICD-9-CM 753.2 including congenital obstruction of the ureteropelvic junction and ureterovesical junction and congenital ureterocele); other anomalies of the kidney and ureter (ICD-9-CM 753.3, 753.4) including double kidney with double pelvis and ectopic kidney, double ureter/ectopic ureter; atresia and stenosis of the urethra and bladder neck (ICD-9-CM 753.6)/hypospadias (ICD-9-CM 752.61); hydroureter (ICD-9-CM 593.5); and hydronephrosis (ICD-9-CM 591). The presence of neuropathic bladder (ICD-9-CM 596.5x), neurogenic bladder due to cauda equina syndrome (ICD-9-CM 344.61), and atony of the bladder (ICD-9-CM 596.4) were also examined. The diagnosis of spina bifida (myelomeningocele) was based on ICD-9-CM code 741. VUR was classified into three categories: primary isolated VUR, primary VUR associated with other CAKUT and secondary VUR as associated with increased intravesical pressure such as stenosis of the urethra and bladder neck or neurogenic bladder.

Clinical Outcomes

The long-term outcomes were the prevalence of hypertension (ICD-9-CM 401.x-405.x), proteinuria (ICD-9-CM 791.0), small kidney (ICD-9-CM 589.0, 589.1, 589.9), and end-stage renal disease (ESRD) (ICD-9-CM 585).

Table 1 Clinical Characteristics of the Children with a UTI with and without VUR

Variables	Total (n=3800)	With VUR (n= 388)	Without VUR (n= 3412)	P value
Male	2119 (55.8%)	226 (58.2%)	1893 (55.5%)	0.298
Median (IQR) age at first UTI (years)	0.5 (0.3–1.2)	0.4 (0.3–0.9)	0.5 (0.3–1.2)	0.235
Age ≤ 1 year at the onset of a UTI	2743 (72.2%)	301 (77.6%)	2442 (71.6%)	0.012
Any CAKUT other than VUR				
Renal agenesis and dysgenesis	16 (0.4%)	8 (2.1%)	8 (0.2%)	<0.001
Cystic kidney disease	6 (0.2%)	0 (0.0%)	6 (0.2%)	1.000
Obstructive defect of renal pelvis and ureter	48 (1.3%)	16 (4.1%)	32 (0.9%)	<0.001
Atresia and stenosis of urethra and bladder neck, hypospadias	21 (0.6%)	7 (1.8%)	14 (0.4%)	0.004
Hydroureter	20 (0.5%)	9 (2.3%)	11 (0.3%)	<0.001
Hydronephrosis	490 (12.9%)	100 (25.8%)	390 (11.4%)	<0.001
Duplex collecting system, ectopic kidney, ectopic ureter	86 (2.3%)	52 (13.4%)	34 (1.0%)	<0.001
Neuropathic bladder	28 (0.7%)	12 (3.1%)	16 (0.5%)	<0.001
Spina bifida	9 (0.2%)	5 (1.3%)	4 (0.1%)	0.001
Clinical outcomes				
Proteinuria	41 (1.1%)	4 (1.0%)	37 (1.1%)	1.000
Small kidney	12 (0.3%)	6 (1.5%)	6 (0.2%)	0.001
Hypertension	15 (0.4%)	3 (0.8%)	12 (0.4%)	0.192
ESRD	14 (0.4%)	5 (1.3%)	9 (0.3%)	0.010

Abbreviations: CAKUT, congenital anomalies of the kidney and urinary tract; ESRD, end-stage renal disease; IQR, interquartile range; UTI, urinary tract infection; VUR, vesicoureteral reflux.

Statistical Analysis

Continuous data were expressed as medians with interquartile range (IQR), and examined using the Mann–Whitney U-test. Categorical data were expressed as numbers and percentages, and compared using Fisher's exact test or the chi-square test. We first compared demographic and clinical data between the VUR and non-VUR groups, and then analyzed sex differences in demographics, comorbidities and outcomes among the children with VUR. Finally, we assessed the risk factors for VUR using univariate and multivariate logistic regression analysis, and odds ratios (ORs) and 95% confidence intervals (CIs) were calculated. Only variables with a $p < 0.05$ in the univariate analysis were included in the multivariate regression analysis. All statistical analyses were performed using SPSS version 21.0. P values of < 0.05 were considered to indicate statistical significance.

Results

Demographics and Clinical Data

The demographic and clinical data of the study subjects are shown in Table 1. A total of 3800 children aged ≤ 6 years with a newly diagnosed UTI were included in the analysis, of whom 2119 (55.8%) were male and 1681 (44.2%) were female. Of these children, 388 (10.2%) had VUR during the follow-up period (226/2119 (10.7%) boys and 162/1681 (9.6%) girls). Three hundred and twenty-nine (84.8%) of the children were diagnosed with VUR ≤ 90 days after the first UTI. The median (IQR) interval between the diagnosis of a first UTI to VUR was 10.0 (0.0, 28.8) days. VUR was diagnosed in 11.0%, 7.2% and 7.5% of the children who were ≤ 1 year of age, 1–2 years of age, and 2–3 years of age at first UTI, respectively. The median (IQR) age at the first recognized UTI for those with VUR was similar to those without VUR (0.4 (0.3–0.9) vs 0.5 (0.3–1.2) years, p=0.235). However, the children with VUR were more likely to have a UTI when they were ≤ 1 year of age (77.6% vs 71.6%, p=0.012). The median (IQR) age at the diagnosis of VUR was 0.5 (0.3–1.3) years. The age distribution at a diagnosis of VUR according to gender is shown in Figure 1. In the children with

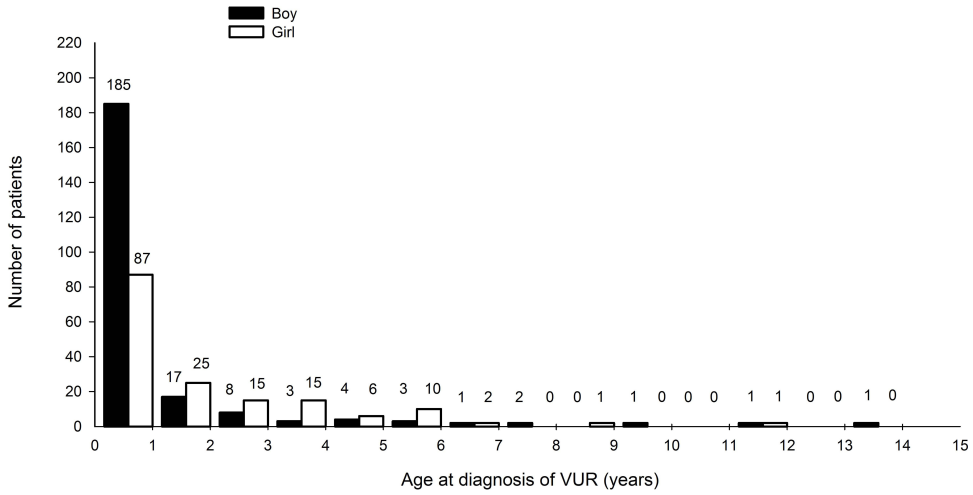

Figure 1 Age distribution at a diagnosis of VUR according to gender.
Abbreviation: VUR, vesicoureteral reflux.

VUR, VUR was diagnosed in 272 (70.1%), 42 (10.8%), 23 (5.9%), 18 (4.6%), 10 (2.6%), 13 (3.4%), 10 (2.6%) at an age of 0–1, >1–2 years, >2–3 years, >3–4 years, >4–5 years, >5–6 years and >6–14 years, respectively. All other forms of CAKUT except VUR were found in 586 (15.4%) of the UTI children. Of the children with VUR, a total of 237 (61.1%) children were diagnosed with isolated primary VUR. Compared to the children without VUR, those with VUR had significantly higher rates of the coexistence of CAKUT including renal agenesis or dysgenesis, urinary tract obstruction such as renal pelvis, ureter, bladder neck and urethra, hydroureter, hydronephrosis, duplex kidney, neuropathic bladder and spina bifida. Of the children with VUR, 1.0%, 1.5%, 0.8% and 1.3% developed proteinuria, small kidney, hypertension and ESRD after a median (IQR) follow-up of 9.6 (6.3–12.5) years, respectively. Compared to the children without VUR, those with VUR were more likely to develop small kidney and progression to ESRD.

Comparison of Demographics and Comorbidities Between the Boys and Girls with VUR

Figure 2 shows the male to female ratio according to the age at the first diagnosis of VUR. VUR was detected more frequently in boys than in girls, with a male-to-female ratio of 1.4: 1. The male to female ratio was 2.1 in the first 12 months, but thereafter VUR was more common in the girls. The results of comparative analysis of demographic characteristics, comorbidities and outcomes in the boys and girls with VUR are shown in Table 2. The boys and girls had a similar interval between the diagnosis of a first UTI and VUR. The median (IQR) age at first UTI in the children with VUR was lower in the males than in the females (0.3 (0.2–0.6) vs 0.8 (0.3–1.9) years, $p<0.001$). The boys with VUR more frequently had a UTI when they were ≤ 1 year of age (89.4% vs 61.1%, $p<0.001$). Furthermore, the median (IQR) age at a diagnosis of VUR was lower in the males than in the females (0.4 (0.3–0.7) vs 0.9 (0.5–2.7) years, $p<0.001$). Compared to the males with VUR, the girls had significantly higher rates of a duplex collecting system/ectopic kidney/ectopic ureter (18.5% vs 9.7%, $p=0.012$), and hydroureter (4.9% vs 0.4%, $p=0.005$). There were no significant differences between the boys and girls in proteinuria, hypertension, small kidney and progression to ESRD during the follow-up period.

Univariate and Multivariate Logistic Regression Analyses of Risk Factors for VUR

As shown in Table 3, age ≤ 1 year at the first UTI, renal agenesis and dysgenesis, atresia and stenosis of the urethra and bladder neck/hypospadias, obstructive defect of the renal pelvis and ureter, hydroureter, hydronephrosis, duplex collecting system/ectopic kidney/ectopic ureter, neuropathic bladder and spina bifida were significantly associated with a higher risk of VUR in univariate analysis. Multivariate logistic regression analysis showed that age ≤ 1 year at the first UTI (OR, 1.3; 95% CI: 1.0–1.7), renal agenesis and dysgenesis (OR, 4.1; 95% CI: 1.3–13.1), hydronephrosis (OR, 2.2; 95% CI:

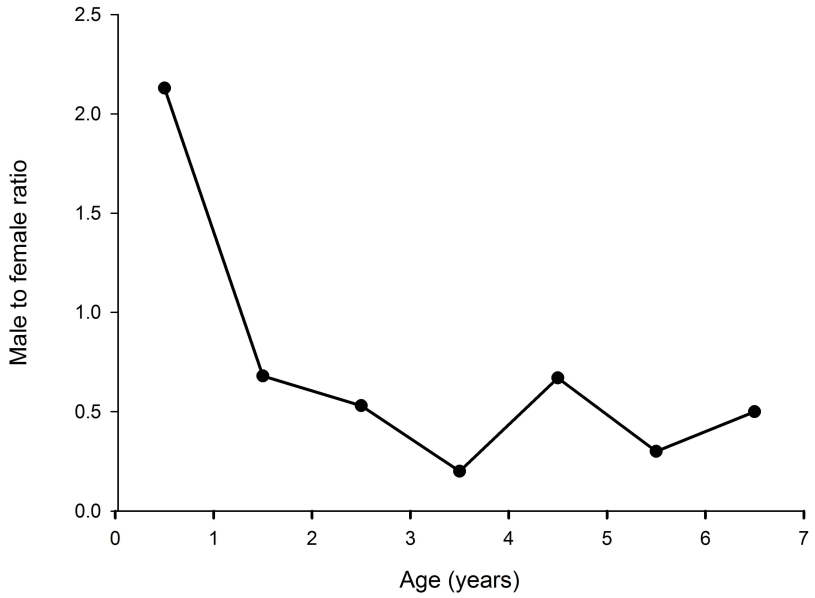

Figure 2 Male to female ratio at their first diagnosis of VUR in children under 7 years.
Abbreviation: VUR, vesicoureteral reflux.

1.7–2.9), duplex collecting system/ectopic kidney/ectopic ureter (OR, 13.0; 95% CI: 8.1–20.8), neuropathic bladder (OR, 4.7; 95% CI: 2.0–11.1) and spina bifida (OR, 5.9; 95% CI: 1.3–27.8) were independent factors for VUR.

Discussion

We carried out a large, population-based study based on a nationally representative subset of the NHIRD. Several studies have demonstrated the validity of diagnosis codes in the NHIRD.[18] The present findings provide clinically applicable information on the risk factors for VUR in children with UTI in countries with a low prevalence of circumcision.

Children with known CAKUT are very prone to develop UTIs. The widespread use of prenatal sonography has resulted in the early detection of CAKUT in the uterus or during infancy. In the present study, 21.9% of the children with a UTI had an identified CAKUT, most commonly hydronephrosis (12.9%) and VUR (10.2%).

Primary VUR is the most common form of reflux and is generally caused by a congenital birth defect of the ureter. It tends to disappear with time, and many children with VUR are asymptomatic. Children with VUR are not usually diagnosed until the occurrence of a UTI or when undergoing an examination to reveal the cause of hydronephrosis. Secondary VUR refers to reflux caused by blockage in the bladder or urethra, and often affects bilateral ureters and kidneys. In the current study, 237 (61.1%) of the children with VUR had isolated primary VUR, and 151 (38.9%) were associated with other CAKUT or secondary VUR. In addition, VUR was found in 10.2% of the children who had a first UTI in the inpatient setting, which is lower than in previous studies on white children with symptomatic UTI. The reported prevalence of VUR has been reported to range from 22–52% in Caucasian populations,[3–6,19,20] and the lowest prevalence of VUR in children with UTI has been reported in black children (5–10%).[3,7,8]

Because of the natural tendency of primary VUR to resolve spontaneously, young children, and especially infants, are more likely to have VUR than older children. Our results showed that the occurrence of VUR in the infants with UTIs was 1.3 times higher than in those > 1 year of age. It is well known that girls are at a much higher risk of having VUR than boys during childhood. In Taiwan, circumcision is not routinely performed in neonates, and the prevalence has been reported to be 7.7% in school-age boys.[21] As a result of possible increased rates of UTIs in uncircumcised infants in Taiwan, more male infants receive screening radiologic studies for CAKUT and VUR in early life when they have a first

Table 2 Comparison of Demographics, Comorbidities and Clinical Outcomes Between the Boys and Girls with VUR

Variables	Boys (n=226)	Girls (n=162)	P value
Median (IQR) age at first UTI (years)	0.3 (0.2–0.6)	0.8 (0.3–1.9)	<0.001
Age ≤ 1 year at first UTI	202 (89.4%)	99 (61.1%)	<0.001
Median (IQR) age at diagnosis of VUR (years)	0.4 (0.3–0.7)	0.9 (0.5–2.7)	<0.001
Median (IQR) interval between the diagnosis of first UTI and VUR (days)	10 (0.0–25.5)	9.5 (0.0–41.0)	0.668
Any CAKUT other than VUR			
Renal agenesis and dysgenesis	5 (2.2%)	3 (1.9%)	1.000
Obstructive defect of the renal pelvis and ureter	8 (3.5%)	8 (4.9%)	0.494
Atresia and stenosis of the urethra and bladder neck, hypospadias	5 (2.2%)	2 (1.2%)	0.704
Hydroureter	1 (0.4%)	8 (4.9%)	0.005
Hydronephrosis	62 (27.4%)	38 (23.5%)	0.377
Duplex collecting system, ectopic kidney, ectopic ureter	22 (9.7%)	30 (18.5%)	0.012
Neuropathic bladder	8 (3.5%)	4 (2.5%)	0.548
Spina bifida	3 (1.3%)	2 (1.2%)	1.000
Clinical outcomes			
Proteinuria	2 (0.9%)	2 (1.2%)	1.000
Small kidney	4 (1.8%)	2 (1.2%)	1.000
Hypertension	2 (0.9%)	1 (0.6%)	1.000
ESRD	4 (1.8%)	1 (0.6%)	0.406

Abbreviations: CAKUT, congenital anomalies of the kidney and urinary tract; ESRD, end-stage renal disease; IQR, interquartile range; UTI, urinary tract infection; VUR, vesicoureteral reflux.

Table 3 Univariate and Multivariate Logistic Regression Analyses for the Risk Factors of VUR

Variables	Univariate		Multivariate	
	OR	95% CI	OR	95% CI
Male sex	1.1	0.9–1.4		
Age ≤ 1 year at the onset of a UTI	1.4	1.1–1.8	1.3	1.0–1.7
Any CAKUT other than VUR				
Renal agenesis and dysgenesis	9.0	3.3–24.0	4.1	1.3–13.1
Obstructive defect of the renal pelvis and ureter	4.5	2.5–8.4	1.3	0.6–2.8
Atresia and stenosis of the urethra and bladder neck, hypospadias	4.5	1.8–11.1	1.9	0.6–6.0
Hydroureter	7.3	3.0–17.8	2.6	0.9–7.3
Hydronephrosis	2.7	2.1–3.5	2.2	1.7–2.9
Duplex collecting system, ectopic kidney, ectopic ureter	15.4	9.8–24.0	13.0	8.1–20.8
Neuropathic bladder	6.8	3.2–14.4	4.7	2.0–11.1
Spina bifida	11.1	3.0–41.6	5.9	1.3–27.8

Abbreviations: CAKUT, congenital anomalies of the kidney and urinary tract; CI, confidence interval; OR, odds ratio; UTI, urinary tract infection; VUR, vesicoureteral reflux.

UTI. This may result in the early recognition of low grade VUR in boys in Taiwan which may not be detected in circumcised boys in Western countries due to asymptomatic and spontaneous resolution. As with previous studies, more males were found to have VUR during the 1st year of life in this study, with a male to female ratio of 2.1:1, although VUR was 1.8 times more common in the females > 1 year of age. Although VUR was detected more frequently in boys

than in girls, we found that gender was not a risk factor for VUR in this study. A previous study reported that infants with CAKUT except for duplicated ureter were more likely to be boys.[22] In the present study, both duplicated collecting system and hydroureter were more prevalent in the girls with VUR. The similar long-term outcomes including proteinuria, small kidneys, hypertension and ESRD in the boys compared to the girls in our observation may be due to the early identification of VUR preventing episodes of UTI and therefore renal scarring in the boys.

The incidence of UTI and VUR is known to be much higher among infants with hydronephrosis. Furthermore, VUR has been reported to be associated with multicystic dysplastic kidney,[23] unilateral renal agenesis,[24] and duplex kidneys[25] in children. However, the role of screening for ipsilateral or contralateral VUR in children with CAKUT is controversial. Previous studies have shown that white children, male gender, age < 1 year, positive family history of VUR, recurrent UTIs, high C-reactive protein or procalcitonin, and bladder bowel dysfunction are risk factors for VUR.[13,26–30] The usefulness of ultrasound or dimercaptosuccinic acid scan as a screening test for either VUR or high-grade VUR is controversial.[11,31] Our results demonstrated that renal agenesis and dysgenesis, hydronephrosis and duplex collecting system/ectopic kidney/ectopic ureter were independent factors for predicting VUR. This indicates the need for routine renal and bladder ultrasound in all young children after a first febrile UTI to detect anatomical abnormalities of the urinary tract system. Furthermore, VCUG should be performed selectively in children with abnormal screening ultrasound findings.

Most children with spina bifida have urological conditions. Nerve damage causes abnormal bladder function resulting in voiding symptoms, urinary retention or overactive bladder. In children with spina bifida and neuropathic bladder, hydronephrosis, VUR and recurrent UTIs always develop in later life. Early therapy with clean intermittent catheterization, antimuscarinic agents and bladder augmentation may prevent kidney damage caused by VUR and UTI.[32] Our results showed a 5.9-fold increased risk of VUR in the UTI children with spina bifida.

VUR increases the likelihood of recurrent pyelonephritis and potentially subsequent renal scarring. Boys tend to have a higher grade of VUR which is found prenatally or during the first year of life, whereas girls usually have a lower grade of VUR which is detected after the first year of life.[17] The long-term sequelae of VUR include proteinuria, hypertension, chronic kidney disease and ESRD. In the current study, the UTI children with VUR were associated with increased risks of small kidneys and progression to ESRD. However, there were no gender differences in the occurrence of proteinuria, hypertension, small kidneys or progression to ESRD in the children with VUR.

A few limitations of the present study should be mentioned. First, NHIRD does not contain information about laboratory tests such as white blood cell count, C-reactive protein and procalcitonin, and clinical symptoms which are known to be potential indicators for the risk of VUR in children with UTIs. Second, despite the comparatively large number of patients with UTIs in this representative cohort, the small sample size of patients with CAKUT may confound our findings. Furthermore, the number of patients with cystic kidney disease was too small to estimate the OR for VUR in this study. Further studies with a large sample size of patients with CAKUT are required to validate our findings. Third, data on VUR grade and unilaterality versus bilaterality were also unavailable in the NHIRD. Three modalities are currently used to diagnose VUR, namely VCUG, radionuclide cystography and voiding urosonography. There are advantages and limitations to the use of each of these techniques, however only VCUG is widely available in Taiwan and covered by the NHI program. As in most studies, the exact percentage of children with VUR may be underestimated in our study, as VCUG is not routinely recommended after a febrile UTI by experts. Furthermore, parents sometimes refuse VCUG despite physician recommendations due to discomfort during urethral catheterization, radiation exposure, risk of catheter-induced UTI, and the development of psychological distress in the children and parents. VUR grade was a predictive factor of VUR spontaneous remission and surgical outcome.[33] However, there were interobserver differences in reflux grade which may have led to significant differences in treatment decisions. In addition, Baydilli et al showed that VCUG-related parameters such as early filling reflux, distal ureteral diameter ratio > 0.24, and delayed contrast drainage of the upper urinary tract had a better predictive power for endoscopic injection success compared to recurrent UTIs and grade of reflux alone.[34] VCUG provides valuable, detailed information to assist physicians to make individualized, risk-based treatment and prevention strategies for children with VUR.

Conclusion

Understanding the risk factors associated with VUR may help to make an early diagnosis and prevent renal damage. Our results imply that renal ultrasound should be performed in all young children after a febrile UTI. VCUG should be recommended for children at high risk of VUR when they are ≤ 1 year of age if they are diagnosed with CAKUT, especially renal agenesis and dysgenesis, hydronephrosis, duplex collecting system/ectopic kidney/ectopic ureter, neuropathic bladder or spina bifida.

Abbreviations

ATC, anatomical therapeutic chemical; CAKUT, congenital anomalies of the kidney and urinary tract; CI, confidence interval; ESRD, end-stage renal disease; ICD-9-CM, International Classification of Diseases, Ninth Revision, Clinical Modification; IQR, interquartile range; LHID 2010, Longitudinal Health Insurance Database 2010; NHI, National Health Insurance; NHIRD, National Health Insurance Research Database; UTI, urinary tract infection; VCUG, voiding cystourethrogram; VUR, vesicoureteral reflux; OR, odds ratio.

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Disclosure

The authors have indicated they have no conflicts of interest for this work to disclose.

References

1. Sargent MA. What is the normal prevalence of vesicoureteral reflux?. *Pediatr Radiol*. 2000;30(9):587–593. doi:10.1007/s002470000263
2. Williams G, Fletcher JT, Alexander SI, Craig JC. Vesicoureteral reflux. *J Am Soc Nephrol*. 2008;19(5):847–862. doi:10.1681/ASN.2007020245
3. Melhem RE, Harpen MD. Ethnic factors in the variability of primary vesico-ureteral reflux with age. *Pediatr Radiol*. 1997;27(9):750–751. doi:10.1007/s002470050217
4. Sciagrà R, Materassi M, Rossi V, Ienuso R, Danti A, La Cava G. Alternative approaches to the prognostic stratification of mild to moderate primary vesicoureteral reflux in children. *J Urol*. 1996;155(6):2052–2056. doi:10.1016/S0022-5347(01)66104-4
5. Stokland E, Hellström M, Jacobsson B, Jodal U, Lundgren P, Sixt R. Early 99mTc dimercaptosuccinic acid (DMSA) scintigraphy in symptomatic first-time urinary tract infection. *Acta Paediatr*. 1996;85(4):430-436. doi:10.1111/j.1651-2227.1996.tb14055.x
6. Zaki M, Mutari GA, Badawi M, Ramadan D, Al deen Hanafy E. Vesicoureteric reflux in Kuwaiti children with first febrile urinary tract infection. *Pediatr Nephrol*. 2003;18(9):898–901. doi:10.1007/s00467-003-1219-9
7. Askari A, Belman AB. Vesicoureteral reflux in black girls. *J Urol*. 1982;127(4):747–748. doi:10.1016/S0022-5347(17)54024-0
8. West W, Venugopal S. The low frequency of reflux in Jamaican children. *Pediatr Radiol*. 1993;23(8):591–593. doi:10.1007/BF02014974
9. Yılmaz S, Özçakar ZB, Kurt Şükür ED, et al. Vesicoureteral reflux and renal scarring risk in children after the first febrile urinary tract infection. *Nephron*. 2016;132(3):175–180. doi:10.1159/000443536
10. Howard RG, Roebuck DJ, Yeung PA, Chan KW, Metreweli C. Vesicoureteric reflux and renal scarring in Chinese children. *Br J Radiol*. 2001;74 (880):331–334. doi:10.1259/bjr.74.880.740331
11. Tseng MH, Lin WJ, Lo WT, Wang SR, Chu ML, Wang CC. Does a normal DMSA obviate the performance of voiding cystourethrography in evaluation of young children after their first urinary tract infection?. *J Pediatr*. 2007;150(1):96–99. doi:10.1016/j.jpeds.2006.09.028
12. Weiss R, Tamminen-Möbius T, Koskimies O, et al.; for the International Reflux Study in Children. Characteristics at entry of children with severe primary vesicoureteral reflux recruited for a multicenter, international therapeutic trial comparing medical and surgical management. *J Urol*. 1992;148(5 Pt 2):1644-1649. doi:10.1016/S0022-5347(17)36993-8
13. Chand DH, Rhoades T, Poe SA, Kraus S, Strife CF. Incidence and severity of vesicoureteral reflux in children related to age, gender, race and diagnosis. *J Urol*. 2003;170(4 Pt 2):1548–1550. doi:10.1097/01.ju.0000084299.55552.6c
14. Faust WC, Diaz M, Pohl HG. Incidence of post-pyelonephritic renal scarring: a meta-analysis of the dimercapto-succinic acid literature. *J Urol*. 2009;181(1):290–297. doi:10.1016/j.juro.2008.09.039
15. Lee YJ, Lee JH, Park YS. Risk factors for renal scar formation in infants with first episode of acute pyelonephritis: a prospective clinical study. *J Urol*. 2012;187(3):1032–1036. doi:10.1016/j.juro.2011.10.164
16. Shaikh N, Ewing AL, Bhatnagar S, Hoberman A. Risk of renal scarring in children with a first urinary tract infection: a systematic review. *Pediatrics*. 2010;126(6):1084–1091. doi:10.1542/peds.2010-0685
17. Yeung CK, Godley ML, Dhillon HK, Gordon I, Duffy PG, Ransley PG. The characteristics of primary vesico-ureteric reflux in male and female infants with pre-natal hydronephrosis. *Br J Urol*. 1997;80(2):319–327. doi:10.1046/j.1464-410X.1997.00309.x
18. Hsieh CY, Su CC, Shao SC, et al. Taiwan's National Health Insurance Research Database: past and future. *Clin Epidemiol*. 2019;11:349–358. doi:10.2147/CLEP.S196293
19. Shah KJ, Robins DG, White RH. Renal scarring and vesicoureteral reflux. *Arch Dis Child*. 1978;53(3):210–217. doi:10.1136/adc.53.3.210
20. Ditchfield MR, de Campo JF, Nolan TM, et al. Risk factors in the development of early renal cortical defects in children with urinary tract infection. *AJR*. 1994;162(6):1393–1397. doi:10.2214/ajr.162.6.8192006

21. Ko MC, Liu CK, Lee WK, Jeng HS, Chiang HS, Li CY. Age-specific prevalence rates of phimosis and circumcision in Taiwanese boys. *J Formos Med Assoc*. 2007;106(4):302–307. doi:10.1016/S0929-6646(09)60256-4
22. Tain YL, Luh H, Lin CY, Hsu CN. Incidence and risks of congenital anomalies of kidney and urinary tract in newborns: a population-based case–control study in Taiwan. *Medicine*. 2016;95(5):e2659. doi:10.1097/MD.0000000000002659
23. Schreuder MF, Westland R, van Wijk JA. Unilateral multicystic dysplastic kidney: a meta-analysis of observational studies on the incidence, associated urinary tract malformations and the contralateral kidney. *Nephrol Dial Transplant*. 2009;24(6):1810–1818. doi:10.1093/ndt/gfn777
24. Song JT, Ritchey ML, Zerin JM, Bloom DA. Incidence of vesicoureteral reflux in children with unilateral renal agenesis. *J Urol*. 1995;153 (4):1249–1251. doi:10.1016/S0022-5347(01)67578-5
25. Thomas JC. Vesicoureteral reflux and duplex systems. *Adv Urol*. 2008;2008:651891. doi:10.1155/2008/651891
26. Nino F, Ilari M, Noviello C, et al. Genetics of vesicoureteral reflux. *Curr Genomics*. 2016;17(1):70–79. doi:10.2174/1389202916666151014223507
27. Leroy S, Adamsbaum C, Marc E, et al. Procalcitonin as a predictor of vesicoureteral reflux in children with a first febrile urinary tract infection. *Pediatrics*. 2005;115(6):e706–e709. doi:10.1542/peds.2004-1631
28. Dick PT, Feldman W. Routine diagnostic imaging for childhood urinary tract infections: a systematic overview. *J Pediatr*. 1996;128(1):15–22. doi:10.1016/S0022-3476(96)70422-5
29. Oostenbrink R, van der Heijden AJ, Moons KG, Moll HA. Prediction of vesico-ureteric reflux in childhood urinary tract infection: a multivariate approach. *Acta Paediatr*. 2000;89(7):806–810. doi:10.1111/j.1651-2227.2000.tb00380.x
30. Sillén U. Bladder dysfunction and vesicoureteral reflux. *Adv Urol*. 2008;2008:815472. doi:10.1155/2008/815472
31. Shaikh N, Spingarn RB, Hum SW. Dimercaptosuccinic acid scan or ultrasound in screening for vesicoureteral reflux among children with urinary tract infections. *Cochrane Database Syst Rev*. 2016;7(7):CD010657. doi:10.1002/14651858.CD010657.pub2
32. de Jong TP, Chrzan R, Klijn AJ, Dik P. Treatment of the neurogenic bladder in spina bifida. *Pediatr Nephrol*. 2008;23(6):889–896. doi:10.1007/s00467-008-0780-7
33. Läckgren G, Cooper CS, Neveus T, Kirsch AJ. Management of vesicoureteral reflux: what have we learned over the last 20 years? *Front Pediatr*. 2021;9:650326. doi:10.3389/fped.2021.650326
34. Baydilli N, Selvi I, Pinarbasi AS, et al. Additional VCUG-related parameters for predicting the success of endoscopic injection in children with primary vesicoureteral reflux. *J Pediatr Urol*. 2021;17(1):68.e1–68.e8. doi:10.1016/j.jpurol.2020.11.018